RENAL FUNCTION

Transactions of the Fifth Conference
October 14, 15 and 16, 1953, Princeton, N J

Edited by
STANLEY E BRADLEY M D
ASSOCIATE PROFESSOR OF MEDICINE
COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS AND SURGEONS
NEW YORK N Y

Sponsored by the
JOSIAH MACY, JR FOUNDATION
NEW YORK N Y

Library of Congress Catalog Card Number 51 33198
Price $3 75

Opinions expressed and any conclusions drawn are those of the participants of the conference and are not to be understood as necessarily having the endorsement of or representing the viewpoints of the Josiah Macy Jr Foundation

Printed in the United States of America
By Corlies Macy & Company Inc New York N Y

PARTICIPANTS

*Fifth Conference on Renal Function**

MEMBERS

ROBERT F. PITTS, *Chairman*
Department of Physiology, Cornell University Medical School
New York, N. Y.

STANLEY E. BRADLEY, *Secretary*
Department of Medicine, Columbia University College of Physicians and Surgeons
New York, N. Y.

ROBERT W. BERLINER
Section on Kidney and Electrolyte Metabolism, National Heart Institute
National Institutes of Health
Bethesda, Md.

FRANCIS BINKLEY†
Department of Biochemistry, Emory University School of Dentistry
Emory University, Ga.

PHYLLIS A. BOTT
Department of Physiological Chemistry, The Woman's Medical College of Pennsylvania
Philadelphia, Pa.

DANIEL C. DARROW†
Department of Pediatrics, Yale University School of Medicine
New Haven, Conn.

WILLIAM DOCK
Department of Medicine, College of Medicine, State University of New York
Medical Center at New York City
Brooklyn, N. Y.

ARTHUR M. FISHBERG
Department of Medicine, Beth Israel Hospital
New York, N. Y.

ROY P. FORSTER
Department of Zoology, Dartmouth College
Hanover, N. H.

ALLAN A. GRAFFLIN
Department of Anatomy, Johns Hopkins University School of Medicine
Baltimore, Md.

JOHN A. LUETSCHER, JR.
Department of Medicine, Stanford University School of Medicine
San Francisco, Calif.

JEAN OLIVER
Renal Research Unit, Overlook Hospital
Summit, N. J.

EWALD E. SELKURT†
Department of Physiology, Western Reserve University School of Medicine
Cleveland, Ohio

---

*This is the final conference
†Absent

JAMES A SHANNON*
National Heart Institute National Institutes of Health
Bethesda, Md

NATHAN W SHOCK
Section on Gerontology National Heart Institute National Institutes
of Health and Baltimore City Hospitals
Baltimore Md

JOHN V TAGGART
Department of Medicine Columbia University College of Physicians and Surgeons
New York, N Y

GEORGE W THORN*
Department of Medicine Peter Bent Brigham Hospital
Boston Mass

GUESTS

ERNEST S BREED
Third Surgical Division New York University College of Medicine
New York N Y

GRAHAM MacGREGOR BULL
Department of Medicine The Queen's University of Belfast
Belfast Northern Ireland

CHARLES H BURNETT
Department of Medicine North Carolina Memorial Hospital
Chapel Hill N C

HENRY D LAUSON
Department of Physiology Cornell University Medical College
New York N Y

JOHN P MERRILL
Department of Medicine Harvard Medical School
Boston Mass

BENJAMIN F MILLER
Department of Medicine Harvard Medical School
Boston Mass

DAVID PRESSMAN
Section of Immunochemistry Sloan Kettering Institute for Cancer Research
New York N Y

ROY C SWAN
Department of Physiology Cornell University Medical College
New York N Y

The Josiah Macy, Jr Foundation
FRANK FREMONT-SMITH, *Medical Director*
JANET FREED LYNCH, *Assistant for the Conference Program**

*Absent



1st Row John A Luetscher, Jr, Graham MacGregor Bull, Roy P Forster, Phyllis A Bott, William Dock, Robert F Pitts, John P. Merrill, Stanley E Bradley, Arthur M Fishberg.
2nd Row Peggy Kubie, Ernest S Breed, David Pressman, Allan A Grafflin, Charles H Burnett, Roy C Swan, Nathan W Shock, Henry D Lauson, Jean Oliver, Robert W Berliner, Benjamin F Miller, Ruth E Rue, John V Taggart

TABLE OF CONTENTS

Fifth Conference on Renal Function

THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

When I was on a destroyer out at Bikini in 1946 I was fascinated listening to our radio operator as he tested communication equipment He would ask another ship through his radio, "How do you hear me?" and the answer often would come back, "I hear you Nine-Nine Nine" That meant that everything was satisfactory. Of the three nines, one was for intensity, one for clarity, and one for meaning

The Josiah Macy, Jr Foundation has organized and devoted a large portion of its resources to the support of its Conference Program because the officers are cognizant of the fact that there is considerable obstruction to communication and mutual understanding across the disciplines and specialties, and that this, in fact, is one of the major factors delaying scientific advancement We feel that there are psychological, as well as semantic factors contributing to the difficulty of communication, people, even in arguments with one another, are too much inclined to make statements *at*, rather than to communicate *with*, others I think that we are inclined to forget, though, that the real question is, are these words and statements those which are likely to convey to the listener the whole or even a small part of what I would like to express

I have a feeling that we should be very much concerned with the other fellow's receiving set and not only with our own transmitter If the other person doesn't seem to understand us, it may not be enough merely to increase the power of our transmission, we must try to find the obstruction in his receiving set, and see what kind of filters and resistors he uses So, if we call out to the interprofessional No-Man's Land, "How do you hear me?" and the reply comes back, "I hear you Nine-Nine Nine," we have the beginning of communication What we try to do in these conferences conducted by the Foundation is to set the stage for meaningful communication

With the accelerating rate at which new knowledge is accumulating and with the increasing recognition that nature is of one piece, it becomes evident that the continued isolation of the several branches of science from one another is a serious obstacle to scientific progress Nowhere in science is the need for "combined opera

tions" more evident than in medicine Today, to be effective, medical research and practice must embrace data from all the disciplines including nuclear physics at one end of the spectrum and cultural anthropology at the other, for advances in one field are frequently dependent upon knowledge derived from quite another discipline

Although the fertility of the multidiscipline approach is thus recognized, universities, and scientific societies and journals which are usually restricted to one small area of a field in their coverage, have not yet made adequate provision for channels of interdisciplinary communication We do not wish to compete with the formal scientific meetings or with the scientific journals which have established patterns and formats for the presentation of material Our purpose at the meetings is to keep an informal atmosphere and to encourage the exchange of methods, research plans, concepts and difficulties, which cannot be done if there is formal speech making

The Foundation has endeavored to meet the need for interdisciplinary communication by bringing together for a series of two-and-a half day annual conferences a small group of investigators, representing in so far as possible all the branches of science related to a chosen problem Participants in these informal conferences over a five year period develop a feeling of friendship, trust and mutual respect which in turn promotes communication, cross fertilization of ideas and cooperation The success of such an endeavor however, is dependent upon full participation of all members in the discussion Accordingly attendance at any conference is limited to twenty-five

Under the guidance of Dr Willard C Rappleye, President of the Foundation since 1942, the Conference Program has been gradually expanded and enlarged until during 1953 it included twelve different groups which meet annually to discuss a wide variety of problems in the field of medicine and the closely related disciplines Our plan is to discontinue the meetings of each group at the end of five years

In order to share with a wider group of investigators and students the essential quality of these conferences and to give others an insight into the functions of the scientific mind, the informal nature and tempo of the discussions, as far as possible, are preserved in the published transactions

FRANK FREMONT SMITH, M D,
Medical Director

THE NEPHROTIC SYNDROME

JOHN A LUETSCHER, JR
Department of Medicine
Stanford University School of Medicine

You ARE ALL familiar with the clinical pattern of the nephrotic syndrome, a disease of undetermined etiology It is sufficiently distinctive so that there is little uncertainty in diagnosis, but it still lacks a respectable name, as Dr Oliver (1) has pointed out to us so forcefully The progression of the disease depends on undetermined factors, and the prognosis is, unfortunately, one of chronic illness in which a large proportion of the patients come to a fatal termination The thought and interest it has aroused are justified, we have some reliable information regarding its physiology, together with methods of modifying the abnormalities However, as yet we do not seem to have an effective method of treatment

There have been some changes in attitude toward the nephrotic syndrome over the past few years There was a time when the disease was considered to affect renal tubules, but now there is an increasing emphasis on the glomerular lesions One sees beautiful demonstrations with the newer stains (2), and with electron photomicrographs in which regular, and perhaps characteristic, morphologic lesions appear in the glomeruli The possibility that the nephrotic syndrome is a disease of immunological origin has been suggested by the similarities of the lesions in man to those which occur in the rat after injection of nephrotoxic serum Dr Pressman's observation (3) that the antibody producing nephrotoxic nephritis is localized in the glomerulus may indicate that we are dealing with a disease which may start in the glomerulus Some of the tubular lesions may be secondary to the primary glomerular lesion

When one turns to the physiology of the disease one finds the widest disparity in renal function, in different cases In the early stages there may be increased or decreased renal blood flow and filtration In the later stages, there is a more uniform reduction in filtration, a low filtration fraction, and variable reduction in maximal tubular capacity

Most of us would agree that proteinuria, which is one of the

more conspicuous features of the nephrotic syndrome, is related to an abnormality of the glomerulus, since the massive quantities of protein appearing in the urine could scarcely be due to a tubular failure of reabsorption of the quantities of protein postulated to be present in normal glomerular filtrate. The edema, which is the second major clinical manifestation of the disease, must be related either to a failure of the glomerular apparatus to filter appreciable quantities of sodium, in excess of the amount removed by obligatory reabsorption in the tubule, or the tubule must be overactive in the reabsorption of sodium. Some of us came rather quickly to the conclusion that since edema occurs regularly and renal blood flow and filtration vary considerably, there must be some factor at work which would increase sodium reabsorption by the tubules of certain patients.

However, this is a matter for speculation. We accept the idea that grossly reduced filtration can impair the ability of the body to eliminate sodium. Experiments by our group and others have shown that the reduced filtration rate which occurs in the nephrotic syndrome can be increased by the intravenous injection of albumin. When a marked increase can be produced, there is an increased excretion of sodium. However, the appearance of sodium in the urine after infusions of albumin is delayed. The increase in sodium output is less than one might expect, if simple imbalance between the glomerulus and the tubule were the sole cause for the sodium reabsorption. Even when the filtration rate is raised to normal or above normal, the elimination of sodium lags for some hours behind the increase in the filtration rate. Because we were disappointed in a simple mechanical explanation, we cast about for possible elements which might stimulate the tubular reabsorption of sodium and became interested in the adrenal cortex.

The work (4) presented to this conference three years ago, on the increased sodium retaining activity of the corticoid fraction of urine in the nephrotic syndrome, has been confirmed by McCall and Singer (5). The increased sodium retaining activity of a similar fraction has also been observed in some other diseases associated with generalized edema (4,6,7,8). We have made further observations on the circumstances in which the sodium retaining activity is increased or decreased and on the nature of the active material. Although these studies are still in progress, it is not amiss to review the present status, particularly in relation to the nephrotic syndrome. You may recall that we presented evidence (4) that most patients with the massive edema of the nephrotic syndrome showed increased sodium retaining activity in the neutral lipid extract of urine.

Editor's Note Dr Luetscher would like to add the following statements to his remarks at the conference

The assay of sodium retaining activity is made on a neutral lipid extract of urine A 24 hour collection of urine is acidified to pH 1 0 and extracted with in one hour with four aliquots of chloroform This extract does not contain all of the sodium retaining activity since additional active material may be extracted after further exposure to acid The data to be presented are based on immediate extraction The chloroform extracts are combined washed with alkali and evaporated to dryness The residue is dissolved in ethanol and aliquots equivalent to a 20 minute collection of the urine are injected into each rat in the bio-assay

The bio assay is made in nine adrenalectomized rats maintained on a controlled intake of sodium Each rat receives on successive days an injection of the control solvent of 5 µg of desoxycorticosterone acetate and of the material to be assayed The response may be calculated on the basis of sodium output or of potassium to sodium output ratio (9) The water loaded adrenalectomized rats respond to 11 desoxycorticosterone and to some closely related compounds including aldosterone with a reduction of sodium output and increased potassium excretion Corticosterone cortisone and hydrocortisone cause an increased output of water sodium and potassium in the assay

Luetscher When such patients were treated with cortisone or ACTH and when diuresis resulted in elimination of edema there was a decrease in the elevated sodium retaining activity however it did not fall when diuresis failed to appear Diuresis following infusion of albumin was accompanied by reduced sodium retaining activity

There are several patterns of clinical response to the administration of the adrenocortical steroids or of corticotrophin When cortisone was administered for 10 to 14 days the patients showed increased proteinuria and edema for a few days Diuresis usually followed after the end of treatment at a time when the eosinophil count was rising rapidly which we interpreted as a sign of release from the effects of cortisone Sodium retaining activity showed the greatest decline during the postcortisone diuresis (10)

When ACTH was administered for 10 to 14 days two patterns were observed (11) Some patients showed no obvious clinical improvement during administration of the hormone but had a profuse diuresis after the end of treatment Others showed gradually increasing diuresis while receiving ACTH resulting in the elimination of edema In both these types of response diuresis was accompanied by a reduction of sodium retaining activity

Striking increases in the rate of glomerular filtration have been observed after treatment with ACTH (12) We have followed the 24-hour endogenous creatinine-chromogen clearances, which give a too-generous estimate of glomerular filtration in the nephrotic syndrome, underestimating the increase of filtration after adrenocortical therapy, but allowing continuity of observation with a minimum of disturbing procedures We had *the impression that* diuresis was associated with increased glomerular filtration, but that the level of the glomerular filtration rate (GFR) might be still far below normal at the time of diuresis

We concluded that there was an association between increased sodium retaining activity, very low sodium output, and edema in the untreated group and in failures of treatment, and between a *reduction in sodium retaining activity, increased diuresis of sodium* and water, and the elimination of edema during or after treatment with ACTH or cortisone These findings seemed to justify some further studies on the nature of the active material, and on its role in the regulation of sodium balance

First, an investigation of the nature of the sodium-retaining material seemed to be in order Active neutral lipid extracts of *urine from patients with nephrotic edema were fractionated by* paper chromatography Figure 1 is a contact print, made in ultraviolet light The lighter areas are shadows showing the position of materials absorbing light near 257 mμ The left-hand strip contains 100 μg of desoxycorticosterone, chromatographed simultaneously with the urine extract on the right-hand strip The toluene and propylene glycol system was used for this separation Desoxy-*corticosterone was recovered from eluates of the* middle area of the standard strip, the corresponding area of the chromatogram of urine extract contained only traces of corticosteroid, and no detectable sodium-retaining activity The active fraction of urine moved more slowly than desoxycorticosterone

Figure 2 shows a similar result when an active extract was compared in a longer run with Reichstein's Compound S, 17-hydroxy-*11-desoxycorticosterone, which is also sodium-retaining in* the bioassay Again the sodium retaining activity of the urine extract moved more slowly than Reichstein's S In Figure 3 the standard is placed on the left-hand part of the chromatogram, and V, D, F, and so on, indicate the positions in which these known compounds would be expected to appear

Pitts The left hand part of that chromatogram is what is obtained with 100 gamma of Compound E?

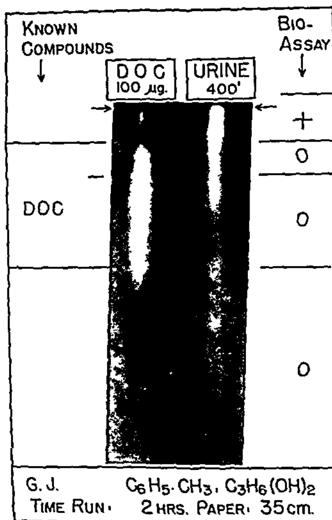
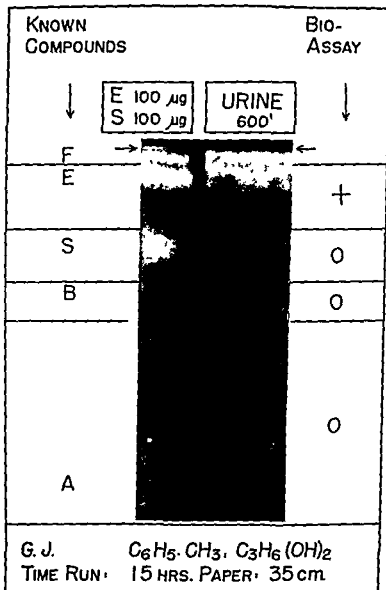


FIGURE 1 Re[illegible] A, Jr, and Johnson, B B Chromatog[illegible] corticoid from the urine of children w[illegible] on normal children *J Clin Investigat*[illegible]



I A Jr and Johnson B B
corticoid from the urine of
on normal children J Clin

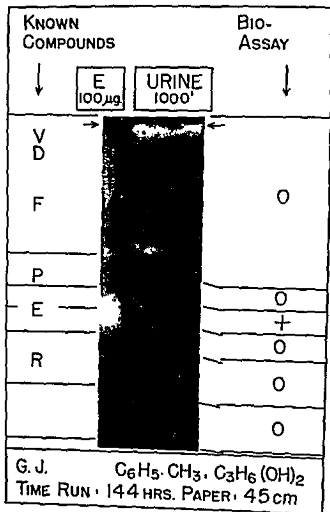


FIGURE 3 Reprinted … I A., Jr, and Johnson B B
Chromato… corticoid from the urine of
children … on normal children J Clin
Investigati…

Luetscher Yes, a little less than one day's urine, extracted and placed on the paper at the starting line on the top The chromatogram developed as the moving solvent flowed down the paper The paper was then dried, photographed, and cut into sections as indicated Eluates from these sections were tested by biological assay Zero or plus at the right represents, respectively, insignificant or significant sodium-retaining activity of the material

When the urine extract is chromatographed for six days in the Zaffaroni system (13), with cortisone as a standard, the sodium retaining activity moves at approximately the same rate as cortisone in toluene propylene glycol, so that the 'cortisone fraction" contains cortisone, the sodium-retaining material, and at least one additional substance This mixture can be separated into its component parts when it is rechromatographed in benzene aqueous methanol

We were in touch with Simpson and Tait (14), who were working on the parallel problem of the separation of the highly active mineralo corticoid of adrenocortical extract They generously informed us that the active material could be separated from cortisone in Bush s system (15) of benzene and aqueous methanol Our experience with the sodium retaining material from urine was the same as their findings with adrenocortical extract

In Figure 4 we see that the active material has now been separated from cortisone The sodium retaining fraction absorbs ultraviolet light with a peak near 240 mμ, reduces tetrazolium and *shows absorption bands in infrared which resembles those given by* corticosteroids with Δ^4 3 keto and 20 keto groupings Per unit of corticosteroid measured, the sodium retaining fraction from urine is 20 times as active as desoxycorticosterone in the bio assay On the basis of these findings (16), we believe that the active material found in urine is of adrenocortical origin, and that it is probably the same as the highly active mineralo corticoid found in adreno cortical extract (14 17,18) and in adrenal venous blood (19,20)

In summary of this phase of the work, all of the significant sodium retaining activity of nephrotic urine can be found in a single *chromatographic fraction which gives the reactions of an adreno*-cortical steroid We shall not be able to prove definitely that it is such a steroid until we have enough material to weigh so as to demonstrate that the activity is not due to a contaminant mixed with some adrenocortical steroid However, the high sodium retaining activity of the final fraction, about twenty times as great as desoxycorticosterone, indicates that we are dealing with a fraction which is not heavily contaminated *with inactive steroid material*

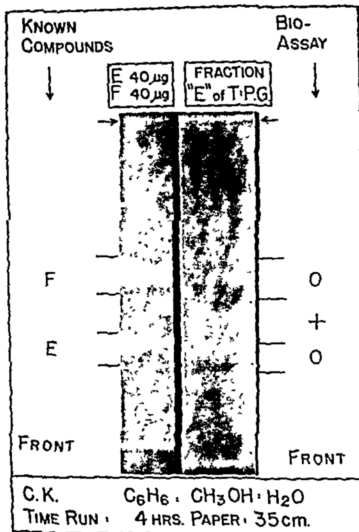


FIGURE 4 Rep... A., Jr., and Johnson, B. B. Chromatograp... corticoid from the urine of children with ... on normal children. J. Clin. Investigation ...

Dock Do you think that this material is not leaking out like protein, but is being overproduced by the adrenal, and that the high levels of the urine, in cases of nephrosis, would also occur, let us say, in cirrhosis and heart failure, when there is water retention? In other pathological conditions, would there be a leak of steroid material like the leak of serum albumin in the nephrotic patient?

Luetscher Whenever we deal with urine, there is a possibility that the level which we measure does not reflect the blood level at that time That is a possible criticism which we must not overlook when we interpret this sort of study

Dock In other cases of edema, and particularly in cirrhosis, there might be no protein in the urine, but you would obtain increased salt-retaining material, would you not?

Luetscher There have been reports that increased sodium-retaining activity of the corticoid fraction exists in cirrhosis, and we ourselves have observed it in cardiac failure and a number of other states associated with edema and difficulty in the elimination of sodium In some instances, there was no obvious impairment of renal function, and proteinuria was minimal or absent I do not believe, offhand, that increased sodium retaining activity of urine represents a leak, but we cannot be sure of that until we have the blood levels

Lauson Am I right in asking whether the steroids that are known to be bound to plasma protein are carried with the beta-lipoprotein? If that is true of your substance, it would seem unlikely that it is carried into the urine attached to beta-lipoprotein, since this globulin is excreted only to a slight extent in the urine of nephrotic patients

Luetscher I think the excretion of beta-lipoprotein in the urine is small, compared with the loss of albumin and of other protein fractions On the other hand, adrenocortical steroids may be dialyzable in a way in which many of the less polar lipids are not The sodium-retaining material in particular, being a relatively more polar substance, probably has an appreciable solubility in water so that it might be expected to be less firmly bound to protein, and, I believe, would probably dialyze off

Figure 5 summarizes the results of chromatography of an actively sodium-retaining extract from a child with the nephrotic syndrome When the neutral lipid fraction is spread out over a number of chromatograms, all the activity of the extract appears in one fraction The dotted lines represent 95 per cent confidence limits, beyond which an assay has a high probability of differing from zero The appearance of all significant sodium-retaining activity in

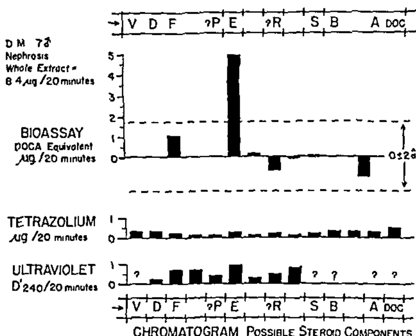


FIGURE 5 Reprinted by permission from Luetscher J A Jr and Johnson B B Chromatographic separation of the sodium retaining corticoid from the urine of children with nephrosis compared with observations on normal children *J Clin Investigation* 33 276 (1954)

this fraction has been characteristic of all extracts in the nephrotic syndrome thus far studied (16) Figure 6 indicates that the corresponding fraction from the urine of a normal child has no significant activity when tested in the same dose

When an edematous patient with the nephrotic syndrome is treated with cortisone or hydrocortisone, a reduction in the output of sodium retaining activity in the urine accompanies the diuresis This reduction can be shown to be due to a parallel change in the activity of the chromatographic fraction which contains the sodium retaining activity in the untreated patient In Figure 7 the sodium retaining activity of the whole extract, and of the cortisone fraction" falls in parallel fashion during and after treatment This change is illustrated in one patient who had a diuresis after administration of cortisone, and in another patient whose diuresis followed treatment with ACTH

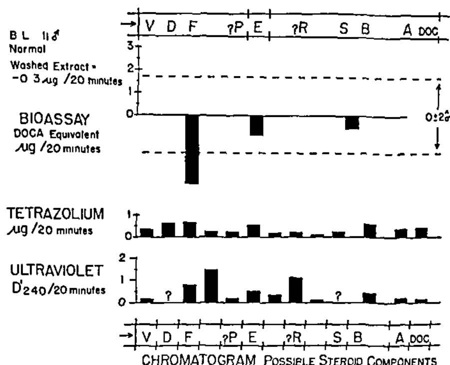


FIGURE 6 Reprinted by permission from Luetscher, J A, Jr, and Johnson B B Chromatographic separation of the sodium retaining corticoid from the urine of children with nephrosis compared with observations on normal children *J Clin Investigation* **33**, *276 (1951)*

Burnett Does this also occur in spontaneous diuresis?

Luetscher We have not had the opportunity of collecting urine during a spontaneous diuresis When observations have been made on edematous patients at one time, and on the same patients at a subsequent time after 'spontaneous" loss of edema, a lowering of the level of sodium retaining activity has been noted

We have been interested to observe the similarity of changes in sodium retaining activity observed after administration of cortisone and ACTH Similar changes have been observed during ACTH therapy Figure 8 illustrates some changes in sodium retaining activity in a patient who had a diuresis during the administration of ACTH The high sodium-retaining activity of the urine extract, and of the *cortisone fraction*, fell during diuresis When the hydrocortisone fraction (*F*) appearing during diuresis was tested, the rats responded with a profuse diuresis of water, sodium, and potas-

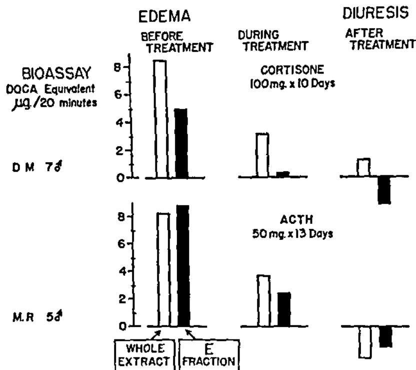


FIGURE 7

sium, which was an interesting, perhaps coincidental, reflection of the patient's high output of water, sodium and potassium at this time

Since a reduction in the sodium-retaining activity of the cortisone fraction occurred either during or after the administration of cortisone or ACTH, and since this reduced activity did not appear to be solely due to competition or interaction with other materials present in the urine, we feel that the regulation of sodium retaining activity is probably separate from the recognized regulation of hydrocortisone secretion by ACTH and that some other regulating factor will have to be sought Aside from the observations on [illegible]

man is placed on a diet of very limited sodium content for a suffi-

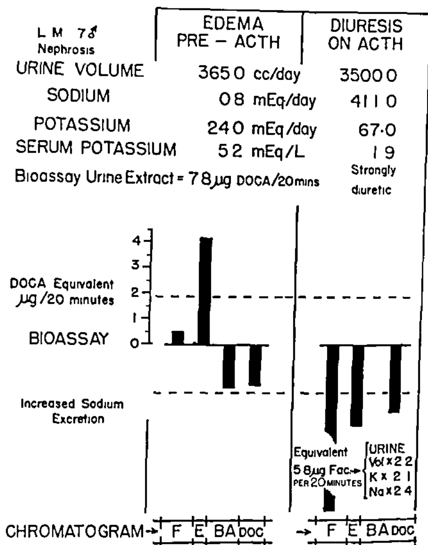


FIGURE 8

cient time to reduce his urinary sodium to a low level, his urine contains increased quantities of sodium-retaining activity The material responsible for the increased activity appears after chromatographic separation in the same fraction as that described in the nephrotic syndrome

Pitts Can the sodium retaining activity be increased by putting

them on a low sodium intake, and depleting them of sodium, say, with diuretics?

Luetscher We have not studied the effects of diuretics in normal subjects, in part because we did not wish to take any chances on modifying renal excretion of the active material The use of a cation-exchange resin might be helpful in producing further depletion Certainly, experiments of that type would be of interest

Burnett Have you found any connection between this and the level of serum sodium?

Luetscher That is a thought that has occurred to us It is true that patients with a reduced serum-sodium concentration are usually those with the most severe nephrotic pattern I am sure there would be a statistical correlation between the serum-sodium level, and the presence of a high level of sodium retaining activity in the urine

Dock An inverse relationship

Luetscher The lower the serum sodium, the greater the probability of finding increased sodium retaining activity We have considered the possibility that reduced serum sodium concentration is a possible stimulus to the output of this material in the urine On the other hand, we have had patients with normal serum sodium levels who have shown increased activity It hardly seems possible that this could be the only stimulus which might set it off

Fishberg What about the correlation between blood volume and activity?

Luetscher We have not measured plasma or blood volume systematically in these patients I dare say that there might be some correlation in the nephrotic, where reduction in plasma volume may be a manifestation of rapid depletion of serum protein On the other hand, if we believe that the blood volume is normal or increased in cardiac failure, we would have difficulty in making the same correlation, because in cardiac failure we may observe an increased excretion of the sodium retaining material

Pitts However, the statement that the output is correlated with the degree of edema is a little ambiguous, is it not? You said that the only thing you knew of that would "turn it on" naturally would be the presence of edema The question is, does that "turn it on," or is edema a result of increased production of sodium retaining material?

Luetscher We should like to think that increased sodium-retaining activity was one of the possible causes of sodium retention and edema That is why we started with the work But we are just n

in a strong enough position to prove anything right now, except that there is activity in certain instances where we might expect it to appear Since we do not yet have supplies of the material sufficient to make the necessary tests in man or in animals, we can define what part it might play only by observation and deduction

Dock You had no opportunity to look for it after severe hemorrhage with shock?

Luetscher We thought we might obtain some volunteers from the blood bank to test normal individuals who had had blood volume reduced acutely in that way However, some technical difficulties arose

Fishberg Is anything known about cardiac output in these children with increased sodium-retaining activity?

Luetscher We have not made such measurements The correlation between the degree of cardiac failure and the cardiac output, as you know, has been a somewhat shaky one One can get into an argument there concerning the adequacy of cardiac output for a given individual at a given time This may be a very difficult question to answer

Dock But many of these patients have quite a good renal blood flow, which presumably means that their cardiac output is not severely impaired It is usually when the cardiac output is down significantly that the renal blood flow falls, too I do not know about the ones you showed us, but many nephrotics have normal renal blood flow, do they not?

Luetscher Clearances may be supernormal in the early stages of the nephrotic syndrome It is difficult to make estimates of cardiac function from renal blood flow when the kidneys are diseased There is also the problem of whether impairment of renal function might alter the output of sodium-retaining material We have felt safe in concluding that the reduced output after cortisone or ACTH represents a change in circulating hormone, since clearances tend to rise at the time when reduced output of sodium-retaining material occurs In the later stages of the disease, with more severe reduction in renal function, the chance of finding increased sodium-retaining activity in the urine becomes progressively less We have found the highest titers in the early stages when renal function tends to be at its best

Dock I wonder whether you have records of observations on patients with chronic Bright's disease? They lose sodium, so when dietary salt is eliminated from their diet, the plasma sodium falls and the blood urea increases rapidly

Another interesting study would be acute hemorrhagic Bright s disease where there is little rise in blood urea when the blood pressure goes up and a modest amount of edema is seen There is an enormous range of disorders to which one could apply this method of assay

Luetscher There is always much more on the agenda than we are able to accomplish

Dock You have a very painstaking time consuming procedure

Luetscher It takes a week to do three assays with our method so we shall have to postpone further experiments until a simpler method is worked out for making these studies perhaps after isola tion and identification

It would be a great advantage to substitute a chemical method for the bio assay however we are in agreement with the conclu sions of Simpson and Tait who see no immediate prospect of doing so The specific activity of the sodium retaining material is so high that very small amounts of hormone are involved Even when an extract is chromatographed twice in different systems there are still traces of inert compounds which contaminate the active fraction Recently we have had the good fortune to receive some 16 alpha hydroxy desoxycorticosterone from Dr Hirschmann (21) and have found that this material has essentially identical chromatographic properties with the active material but it is inert in the bio assay

Dock Is this the same salt retaining material that has been re ported recently from the renal veins of dogs?

Luetscher I am sure that it is

Dock Per microgram that is supposed to be from five to ten times as potent as desoxycorticosterone is it not?

Luetscher I think that Farrell s material contains the same active substance that Simpson and Tait have obtained from adrenocortical extract and which we obtained from human urine

Berliner What proportion of patients with edema have increased activity in the urine?

Luetscher I can answer your question only in terms of our experience with the nephrotic syndrome and cardiac failure and in a few related conditions In the presence of generalized edema of a fairly severe grade with a urine sodium of less than 10 mEq per L most patients would have a measurable increase of sodium retaining activity The low sodium content of urine is a better index than the presence of edema since edema may be present even when diuresis is increasing It would be quite unreasonable if every

in a strong enough position to prove anything right now except that there is activity in certain instances where we might expect it to appear Since we do not yet have supplies of the material sufficient to make the necessary tests in man or in animals we can define what part it might play only by observation and deduction

Dock You had no opportunity to look for it after severe hemorrhage with shock?

Luetscher We thought we might obtain some volunteers from the blood bank to test normal individuals who had had blood volume reduced acutely in that way However some technical difficulties arose

Fishberg Is anything known about cardiac output in these children with increased sodium retaining activity?

Luetscher We have not made such measurements The correlation between the degree of cardiac failure and the cardiac output as you know has been a somewhat shaky one One can get into an argument there concerning the adequacy of cardiac output for a given individual at a given time This may be a very difficult question to answer

Dock But many of these patients have quite a good renal blood flow which presumably means that their cardiac output is not severely impaired It is usually when the cardiac output is down significantly that the renal blood flow falls too I do not know about the ones you showed us but many nephrotics have normal renal blood flow do they not?

Luetscher Clearances may be supernormal in the early stages of the nephrotic syndrome It is difficult to make estimates of cardiac function from renal blood flow when the kidneys are diseased There is also the problem of whether impairment of renal function might alter the output of sodium retaining material We have felt safe in concluding that the reduced output after cortisone or ACTH represents a change in circulating hormone since clearances tend to rise at the time when reduced output of sodium retaining material occurs In the later stages of the disease with more severe reduction in renal function the chance of finding increased sodium retaining activity in the urine becomes progressively less We have found the highest titers in the early stages when renal function tends to be at its best

Dock I wonder whether you have records of observations on patients with chronic Bright s disease? They lose sodium so when dietary salt is eliminated from their diet the plasma sodium falls and the blood urea increases rapidly

Another interesting study would be acute hemorrhagic Bright s disease where there is little rise in blood urea when the blood pressure goes up and a modest amount of edema is seen There is an enormous range of disorders to which one could apply this method of assay

Luetscher There is always much more on the agenda than we are able to accomplish

Dock You have a very painstaking time-consuming procedure

Luetscher It takes a week to do three assays with our method so we shall have to postpone further experiments until a simpler method is worked out for making these studies perhaps after isolation and identification

It would be a great advantage to substitute a chemical method for the bio assay however we are in agreement with the conclusions of Simpson and Tait who see no immediate prospect of doing so The specific activity of the sodium retaining material is so high that very small amounts of hormone are involved Even when an extract is chromatographed twice in different systems there are still traces of inert compounds which contaminate the active fraction Recently we have had the good fortune to receive some 16-alpha hydroxy desoxycorticosterone from Dr Hirschmann (21) and have found that this material has essentially identical chromatographic properties with the active material but it is inert in the bio assay

Dock Is this the same salt retaining material that has been reported recently from the renal veins of dogs?

Luetscher I am sure that it is

Dock Per microgram that is supposed to be from five to ten times as potent as desoxycorticosterone is it not?

Luetscher I think that Farrell s material contains the same active substance that Simpson and Tait have obtained from adrenocortical extract and which we obtained from human urine

Berliner What proportion of patients with edema have increased activity in the urine?

Luetscher I can answer your question only in terms of our experience with the nephrotic syndrome and cardiac failure and in a few related conditions In the presence of generalized edema of a fairly severe grade with a urine sodium of less than 10 mEq per L most patients would have a measurable increase of sodium retaining activity The low sodium content of urine is a better index than the presence of edema since edema may be present even when diuresis is increasing It would be quite unreasonable if every

in a strong enough position to prove anything right now except that there is activity in certain instances where we might expect it to appear Since we do not yet have supplies of the material sufficient to make the necessary tests in man or in animals we can define what part it might play only by observation and deduction

Dock You had no opportunity to look for it after severe hemorrhage with shock?

Luetscher We thought we might obtain some volunteers from the blood bank to test normal individuals who had had blood volume reduced acutely in that way However some technical difficulties arose

Fishberg Is anything known about cardiac output in these children with increased sodium retaining activity?

Luetscher We have not made such measurements The correlation between the degree of cardiac failure and the cardiac output as you know has been a somewhat shaky one One can get into an argument there concerning the adequacy of cardiac output for a given individual at a given time This may be a very difficult question to answer

Dock But many of these patients have quite a good renal blood flow which presumably means that their cardiac output is not severely impaired It is usually when the cardiac output is down significantly that the renal blood flow falls too I do not know about the ones you showed us but many nephrotics have normal renal blood flow do they not?

Luetscher Clearances may be supernormal in the early stages of the nephrotic syndrome It is difficult to make estimates of cardiac function from renal blood flow when the kidneys are diseased There is also the problem of whether impairment of renal function might alter the output of sodium retaining material We have felt safe in concluding that the reduced output after cortisone or ACTH represents a change in circulating hormone since clearances tend to rise at the time when reduced output of sodium retaining material occurs In the later stages of the disease with more severe reduction in renal function the chance of finding increased sodium retaining activity in the urine becomes progressively less We have found the highest titers in the early stages when renal function tends to be at its best

Dock I wonder whether you have records of observations on patients with chronic Bright s disease? They lose sodium so when dietary salt is eliminated from their diet the plasma sodium falls and the blood urea increases rapidly

affecting electrolyte activity and is not simply a toxic agent The potassium sodium ratio has actually been used as a basis for the assays which have been presented here

Lauson If I am not mistaken, reduction in GFR alone, in the absence of change in adrenocorticoid secretion, will result in a relative increase in potassium and decrease in sodium excretion It would be most helpful to prove that GFR does not decrease in rats injected with the urinary steroid I would not be satisfied with the idea that obtaining a reciprocal change in excretion of potassium and sodium necessarily rules out a decrease of GFR following the injection of the extract

Luetscher When you did your experiments in dogs, did you calculate the absolute quantities of potassium which were excreted? Of course, you were using loading experiments at that time, were you not?

Lauson Yes I only wish to point out that I am skeptical about the specificity of the assay in the absence of determinations of GFR Actually, there is no good reason to believe that GFR would decrease after injection of the substance

Pitts As a first approximation, would the rate of creatinine excretion give you essentially the same type of information?

Lauson It would probably be adequate and is much simpler to measure

Pitts That is done by blocking off these urine collections and just measuring creatinine content?

Luetscher Yes

Dock In the dog, it would be a relatively simple procedure as compared with the rest of the assay

Luetscher Yes, I think that should be done

EDITOR'S NOTE Dr Luetscher would like to add the following comments to his remarks at the conference

Sala and Leutscher* found that clearance of creatinine chromogen in adrenalectomized rats under conditions of the bioassay was lower than in normal rats under similar conditions Desoxycorticosterone and aldosterone reduced sodium output without significant change in creatinine clearance The same result was noted on administration of the sodium retaining corticoid from the urine of a patient with nephrosis

Dock Dr Pitts, do you think we should get away from the end result of the nephrotic syndrome, which apparently parallels the

*Unpublished data

edematous patient had a very high output of this material Then, too, there are other factors concerned in the production of general edema, and there are conditions which might impair its excretion in the urine, even if it were circulating in the blood

Merrill Have you had the experience of being able to increase the titer of this active substance in a patient already showing edema, by further restricting his sodium intake?

Luetscher Yes, we have

Merrill And it does go up?

Luetscher It goes up a little further There must be some sort of top limit, since there are some patients with very high initial activity whose levels do not go up appreciably when sodium intake is reduced

Lauson I wonder if we could discuss for a moment the assay itself, since in the end all interpretation depends on that I wonder if by now you have made measurements of GFR in the assay rats before, during, and after injection of either the test or standard substances? The reason I ask is, I think, fairly obvious If GFR were significantly reduced after the injection of urinary extract, this alone could result in salt retention in the animal Eventually, it seems to me, possible changes in GFR will have to be taken into account in the assay of urine for the content of this steroid as well as of antidiuretic substances As far as known, GFR has not been measured during antidiuretic assays in the rat, and I have not heard whether your group has done so

Luetscher That is a most important point I did not go into the assay in any detail, because one can get farther and farther away from the nephrotic syndrome But if we are using an assay which depends on sodium alone, then we may fall into a possible trap all we would have to do would be to give bichloride of mercury, or shoot the rat through the heart, and obviously a maximal reduction in the sodium excretion would occur during that experiment In order to defend ourselves against that criticism, we have to have some kind of routine control In this bio assay, we have used potassium If we use the sodium to-potassium ratio as a measure of activity, we are protected from that type of error

Lauson You mean that more potassium and less sodium is excreted by the test rat?

Luetscher If the tested material stimulates the excretion of potassium to the same extent that it reduces the excretion of sodium, there is a high probability that the substance is one specifically

Dock I think the clinicians would define nephrosis nowadays as any chronic proteinuria in which the patient had neither heart failure nor many red cells in the urine The patient need not be edematous to have a disease such as this over a long period of time, the examination of the urine would show that there was a lesion of this type, although the plasma protein might not have dropped low enough for him to have developed edema

Oliver I have often wondered why some word that makes use of the term "proteinuria" was not applicable to these multiple disturbances in the kidney?

Bull Your definition would include postural proteinuria, would it not?

Dock Yes, certainly It is typical nephrosis

Luetscher "The nephrotic syndrome," so called, is a perfectly good clinical entity There are a number of different pathological lesions which can lead to a similar clinical pattern, but many of them may be distinguished One is faced with the problem of having a clinical lesion, as it were, which is readily definable, and yet having no agreement on the basic pathological difficulty from which the patient suffers

Oliver I think this confusion is definitely the fault of the group to which I belong As you say, there is a clinical situation that deserves some name, but the pathologists have insisted that it must be a "disease of the tubules" It seems to me obvious that it is not

Pitts Does a normal rat have nephrosis? It has proteinuria, does it not?

Oliver Yes it has a "nephrosis," which I suppose, is part of its normal history

Miller We should not confuse the issue further by including the proteinurias, because there can be every clinical variety of this disease One of the difficulties is that some of these acute "nephroses," which are misnamed, as Dr Oliver has pointed out, come into the picture Why not simply agree on the term "chronic nephrotic syndrome," and stress the word, "chronic"? I think we should know what we meant clinically, the pathological picture is fairly well defined

Dock I think Dr Volhard referred to these episodes, occurring in glomerulonephritis as the *nephrotische Einschlage*, or complications

Luetscher I have emphasized one aspect of the problem in which we are interested but I am sure there are many other reasons why a tubule might be hyperactive Dr Lauson has brought out the

phenomenon of cirrhosis and heart failure, and return to something that Dr Luetscher mentioned earlier? There are now more and more histological studies on the glomerular membrane, and some people regard any visible change as perhaps causative, or related to the cause of proteinuria I gather that one school of histologists, believes that what we see in between the two layers of the glomerulus in nephrosis is exactly the same sort of material that we see in the tubule cells in that disease It is not the cause of the leak, but has accumulated because of the leak Is that correct, Dr Oliver?

Oliver Yes

Dock Such lesions have no significance in the etiology of proteinuria We used to think that the tubular lesion was the cause of the proteinuria, but we have more or less abandoned that idea Now we are considering the possibility that the glomerular lesion is the cause of the proteinuria, whereas, just like the tubular lesion, it might be the result of altered permeability with colloidal material accumulating in the ground substance

Oliver I think it is a mistake to suppose that the glomerular lesions were not seen early in the history of nephrosis The very first cases that were described had glomerular lesions, but, as Dr Dock says, the difficulty is in deciding whether these lesions are simply the expression, or the result, of the passage of plasma constituents such as protein or lipid – nobody has said anything so far about lipid – through a damaged membrane, or whether these appearances are the cause of the leakage I do not think anyone can say, but from the beginning there was strong evidence that the effects were not simply a tubular disturbance, but also a glomerular disorder

Dock Dr Fahr (22) resisted this vigorously up until the late forties, I believe

Oliver Nevertheless, I think that the early descriptions of nephrosis showed very definite lesions in the glomerulus One of the three cases that I have called "nephrosis" has extreme changes in the glomerulus

Dock That is something Dr Bell emphasized a long time ago

Oliver Yes, so the statement one authority has made, that nephrosis is "tubular disease," seems to me to be entirely lacking in reality I am interested that Dr Luetscher always used this word as an adjective he says 'the nephrotic syndrome" That is perfectly proper usage It is when we begin using "nephrosis" as a noun, that we produce intellectual confusion

inflating a balloon catheter in the aorta would reduce sodium excretion essentially to zero

Dock I prefer to study my patients, with them one can allow enough time for whatever adrenocortical activity they had to disappear I do not know whether the dogs have it or how fast it wears off When you give a test dose to an animal, how long is it before the tubular effect is exhausted?

Luetscher When material is injected the duration of action varies from a few hours to a day, depending on dosage and rate of absorption We have no data on endogenous secretions I think that all of us have been aware that there are probably at least two possible phases through which an animal might go Practically all the experiments which are related to acute reduction of filtration rate, and blood flow in animals have shown a tendency for a readjustment to occur as time has passed, so that a maneuver which would reduce filtration and excretion of sodium ends up some hours, or a day, later with a preparation in which the filtration rate is still low even though improved to some degree but in which a larger amount of sodium is eliminated The question should be raised as to whether undue emphasis on acute experiments might lead us to overestimate the effect of changes in filtration rate on the sodium excretion, and to overlook compensatory factors which enter in at a later stage

Bott Dr Luetscher, I believe you said that when the sodium level in a patient was low you often found him to be quite ill, and that these patients were putting out a large amount of the hormone which you were investigating Is that correct?

Luetscher Yes, in a spontaneous, natural experiment

Bott And then, after the increased output of the hormone, does the plasma sodium level increase again or does the sodium all go into the tissues? Do you obtain more and more edema?

Luetscher Most of the patients had struck a rough balance with their disease at the time they were observed Some of them were slowly accumulating edema, while others had a stationary level of edema on a reduced sodium intake I do not believe that there is any physiological mechanism for sodium retention which cannot eventually be brought into balance by an accumulated excess of sodium in the body

Bott Can you say whether these patients, showing the lowest plasma sodium level, have lowered glomerular filtration rates?

Luetscher In general that is what we observed Occasionally one sees patients with normal or supranormal filtration rates when

concept that the tubular activity may be increased in certain circumstances, and particularly in these patients I wish he would say something about other possible mechanisms of overactivity of tubules, or other matters which might lead to glomerulotubular imbalance with respect to sodium

Lauson I have not much to add to our recent review (23) of this subject The idea that acute reduction in GFR can result in an excessive reabsorption of salt and water in the dog is well established Glomerular insufficiency as a cause of excessive reabsorption of these substances is therefore a possibility in the nephrotic syndrome If that much be conceded, a corollary must also be conceded, namely, that this type of imbalance may be present to such an extent that no matter how much salt-retaining, or antidiuretic, hormones act upon the tubule, such additions might have little effect In this sense, hypersecretion of these hormones, if eventually proved to occur in patients with the nephrotic syndrome, may turn out to be of secondary importance These statements are, of course, no more than opinions

Dock If we study adrenalectomized animals, or men, perhaps we shall come to the opposite conclusion, that once the adrenals are gone, no matter how low the glomerular filtration rate goes, the kidney is still eliminating sodium

Lauson The amount eliminated is less when GFR is low

Dock But it is still too much

Bradley Will an adrenalectomized animal continue to lose sodium independently of changes in the filtration rate?

Merrill We had one patient who had been adrenalectomized for hypertension, developing in the course a nephrotic syndrome with chronic renal failure, who had a filtration rate of about 20, and showed a marked sodium diuresis without any change of filtration rate during the adrenalectomy

Dock Some of our patients with Addison's disease, in shock, were still losing sodium I am fairly certain that this is true in the adrenalectomized man no matter how low the filtration rate becomes, up to the point of impending death sodium is eliminated in the urine in much greater quantities than it should be There will be a low plasma sodium level, and a considerable amount of sodium in the urine

Pitts There is always the danger in inferring that the results of acute experiments will be the same as those observed in chronic experiments However, Thompson (24) observed in adrenalectomized dogs that an acute reduction in filtration rate produced by

[illegible] filtration rate is normal or almost

at least temporarily, and under those circumstances there seems to be a tendency to water and salt retention I am certainly inclined to believe that reductions in filtration rate may alter the output of a given load of sodium I do not think we can say flatly that there is absolutely no relationship between filtration rate and sodium excretion Undoubtedly this effect of lowered filtration may be entirely masked, blocked, or reversed by a variety of other factors The situation in any given clinical condition has to be evaluated as a whole

Dock When the adrenals are present in the animal, or in man, what has been stated is quite true However, it has not been proved that sodium excretion can be inhibited in the absence of the adrenals Since the adrenals have to be there when one studies this phenomenon in the intact animal, we do not know whether the adrenal cortex is also stimulated by the factors which cause a fall in the glomerular filtration rate That is a problem that has to be solved A tubular cell sensitized by a given amount of material coming from the adrenal may behave in one way, but once that substance has been removed, the tubular cell may be quite indifferent to the amount of sodium that is presented to it

Pitts That has already been done Dr Dock Exactly the same response was obtained with an adrenalectomized animal as with a normal animal

Dock And no adrenal support given?

Pitts No, but that is not the point If we work on an adrenalectomized animal with a good filtration rate to start with there has to be some adrenal support, but there is no chance for that support to vary, during the course of the experiment as a consequence of reduction in filtration rate

Dock I do not think it varies in the acute experiment either

Pitts I think we are getting into a bit of a trap here, in assuming that some of us believe that the filtration rate is everything, or, on the other hand, that the hormonal control of renal tubular function is everything I do not believe that anyone present believes either one of those statements We know that both factors operate

Luetscher In attempting to assess the possible effect of adrenocortical secretion in producing the changes that we see in the nephrotic syndrome, we were interested in the tendency of these patients to cover their excretion of anion with potassium, am-

accumulation of edema is occurring but these patients usually have a normal serum sodium concentration. When we were studying the effects of concentrated human serum albumin in the nephrotic syndrome (25) we noted that water diuresis regularly accompanied the increased plasma volume and filtration rate after intravenous albumin. A rise in serum sodium concentration occurred after this diuresis if the initial level was subnormal. We had the impression that reduced glomerular filtration and impaired water excretion occurred together, perhaps associated with reduced plasma volume, and that all three abnormalities were improved immediately after injection of albumin. Sodium excretion increased so sluggishly and irregularly, even when the tubular load of sodium was raised to a normal level, that we felt that there was some abnormal stimulus to sodium reabsorption which we had failed to modify in acute experiments. To be fair we must point out the statistical correlation between the level of the glomerular filtration and the ability of that patient to excrete sodium. There is no question but that the patients with very low filtration rates have a strong tendency to hold on to sodium and that as the filtration rate increases there is an increasing *probability that the patient will be able to excrete sodium* normally or rid himself of the excess of sodium which has accumulated in the body.

Miller Do you apply that just to nephrotics, Dr Luetscher? Is it not true that there are many patients with severe anemias with marked reduction in glomerular filtration rate who show no tendency toward edema? I have been greatly troubled by this so called imbalance between the glomerular filtration rate and the tubules and have tried to think of other clinical conditions that might teach us something. I am sure that the one which Dr Dock brought up is perfectly valid, that you see patients with Addison's disease in whom there is no such statistical relationship. I have often wondered about some of the patients before the final failure in pernicious anemia *in the years before there was adequate therapy*.

Dock They begin to accumulate edema eventually.

Miller Eventually, yes, but that is terminal, is it not?

Dock It is probably true that their glomerular filtration rate is *down at the critical level*.

Miller I think it falls a good deal before then, though I am not sure about it. I have wondered if this so called statistical relationship would apply only to the particular cases the investigators have been interested in and would break down if other clinical conditions were considered.

monium, and hydrogen ion, instead of sodium This can be most strikingly brought out in patients who are loaded with anion which has to be excreted at a rapid rate A similar tendency in the animal with reduced glomerular filtration has been described by Lauson and Thompson (26) Is this simply a measure of the intensity of the stimulus to sodium reabsorption, regardless of cause or mechanism? Does this same phenomenon occur in an animal receiving a very large dose of desoxycorticosterone, which is sufficient to cut off his sodium excretion?

Berliner I think the answer is "yes"

Luetscher The excretion of other cations could be increased in any situation in which there is the necessity to cover an excreted anion load when sodium is not appearing in the urine, whether because of reduced filtration or increased reabsorption of sodium

Berliner I would put it differently, but I think that your statement describes the results I would be inclined to say that the increased excretion of potassium, ammonium and hydrogen ions are manifestations of the reabsorption of sodium

Lauson Dr Burnett (27,28) presented data here a few years ago which concerned this very point When a normal subject was given a large load of sodium para aminohippurate after pretreatment with ACTH, the urinary anions were accompanied by relatively more potassium and less sodium than when the same subject was similarly loaded in the absence of the exogenous hormone

While we are on the subject of sodium excretion in relation to GFR and tubular reabsorptive factors, I have some thoughts which are probably not very original but which may be helpful In the data of Thompson and Pitts (24), for example, from experiments in which GFR in dogs was acutely lowered, we could draw a smooth curve relating sodium excretion on the ordinate to GFR on the abscissa The curve would show the well known and disproportionately large decrease in sodium excretion that occurs when GFR is reduced Relatively small increase in GFR above control is similarly associated with a disproportionately large increase in sodium excretion This fundamental relationship between sodium excretion and GFR is modified by influences affecting the tubules directly. An excess or absence of salt-retaining adrenal steroids, for example, during the time that GFR is changed artificially, would generate a new curve respectively below and above the original curve These would define a lower and upper envelope of what could be thought of as a family of curves If this concept is reasonably correct, it would follow that, for a given GFR, the absolute range of sodium

after treatment with ACTH or cortisone, it is probably that the inulin clearance would have shown an increase also, perhaps of even greater extent

Pitts Dr Swan has brought up a point of some pertinence to our discussions which he would like to have considered

Swan Would it be appropriate for this group to enumerate which of the points used to substantiate the inulin clearance as a measure of glomerular filtration in the normal person have been systematically confirmed in patients with renal disease, particularly patients with nephrosis? In the foregoing discussions the inulin clearance as a measure of glomerular filtration rate in renal disease, has been generally accepted

Bott There is little published work on that subject, but I think there are a few articles suggesting that there is some reabsorption or back diffusion of inulin in such states

Swan Are you referring to the study of Redish (33)?

Bott I think that is one of them

Lawson Dr Mattar, working with Barnett, McNamara and myself (34) did several experiments in children with renal disease One approach was to measure the inulin clearance at three widely different plasma concentrations of inulin in two nephrotic children and one normal child It was found that in all three the excretion of inulin plotted against plasma concentration was a linear relationship extrapolating through the origin as it should have if there were no significant tubular reabsorption or excretion of the inulin In experiments of another kind it was found that carinamide, in doses which did not affect the elevated ratio of the clearance of specifically determined creatinine to that of inulin, depressed the clearance of PAH to below creatinine but not below inulin A third line of evidence suggesting that inulin measures the glomerular filtration rate (GFR) in children with renal disease is the fact that thiosulfate/inulin clearance in 36 observations on 25 children with renal disease ranged from about 0 75 to 1 25, with an average close to 1 0 for a range of inulin from 5 to 160 ml/min per 1 73 M^2 In 11 normal children, creatinine/inulin clearance averaged 1 03 ± 0 11, whereas in 105 observations on 57 children with renal disease, the ratio varied from the normal range to as high as 2 2 the ratio tended to increase as inulin (in ml/min per 1 73 M^2) decreased None of these lines of evidence by itself is very conclusive but when they are all together they strongly suggest that the inulin clearance is an adequate measure of GFR in patients with renal disease

Dock These were patients with proteinuria?

of creatinine and have obtained quite different numerical results, as reported by many other observers *The nephrotic syndrome is an* especially poor setting in which to use the creatinine clearance as a numerical measure of glomerular filtration On the other hand, the measurement of inulin clearance is limited to a few hours under artificial conditions, and in the nephrotic syndrome I have seen such large changes in creatinine clearance occur during the infusion of inulin that I felt that the results were difficult to interpret I believe that if we wish to find a numerical value for a given instant, we must use inulin When we follow variations over long periods we use creatinine, but obviously we cannot equate the creatinine clearance with the filtration rate

Miller What troubles me is that the endogenous creatinine clearance can be influenced by tubular mechanisms, and if we are looking for changes in these mechanisms, we may find large errors Those of us who know all the difficulties in the creatinine clearance keep these thoughts clearly in mind, but frequently other people use it as a precise measure I am amazed at some of the calculations that have appeared in the literature, basing exact measurements on the endogenous creatinine clearance The exogenous creatinine clearance may be 50 per cent off, and in some instances 100 per cent

I think I am justified, after having put in so many years trying to develop techniques for the measurement of the endogenous creatinine clearance, to point out that the work of J Sirota and J Brod was limited to a certain area, but the moment we leave that area the measurement may become completely valueless I think the paper that Alexander Leaf, A R Mamby, Zelma Miller, and I (31) published recently, showed that rather clearly There are just too many conditions in which the endogenous creatinine clearance does not measure the filtration rate, to make it worth while as a procedure I agree with Dr Luetscher that if we clearly state the difficulties, then we are justified in employing it in certain situations

Lauson In Dr Luetscher's studies, the endogenous creatinine clearance tends to underestimate the increases in GFR resulting from therapy The untreated nephrotic patient usually has an increased creatinine inulin clearance ratio, in some cases greater than 2 0 This is brought out particularly if a specific method is used for creatinine determination (32) After treatment with ACTH or cortisone, the tendency is for this ratio to decrease toward the normal value of about 1 0 (12) Therefore when creatinine clearance, as measured by Dr Luetscher's group, increased during and

ureter that went into the jejunum As far as tests on the patient go, everything that is excreted by the latter is reabsorbed above the bladder The same thing happens with extravasation into the kidney

Berliner I think if you could collect from the ureter before it emptied into the jejunum it would be interesting

Bull When Bywaters was doing some work on the crush syndrome, he took the lymph glands from near the kidney, draining the kidney, and found that the urea content was higher than in the plasma Possibly we could give inulin and sample a lymph gland, then we would see if there was anything partly concentrated and diffusing back

Oliver The holes in the kidney tubule are plainly evident

Dock The man who is working with inulin clearances believes that the glomerular filtration rate is down, when, as a matter of fact, all that has happened is that the tubule acts like a leaky hose He calls this a low glomerular filtration rate, when actually he has not come anywhere near to measuring glomerular filtration, because between his collection and the glomerulus there is a hole in the hose That is the whole point There is no way of testing for this except obtaining lymph from the patient s lymph node

Suan How about nephrosis, where we do not have a histologically demonstrable hole?

Oliver In such cases we have an experimentally demonstrated change in the epithelium, so that a very large molecule like trypan blue can be seen to have diffused into the cell, discoloring diffusely the whole tubular wall (35) We do not need a hole to obtain leakage, but I was speaking of the extreme case where there *is* a hole

Dock Dr Bull suggested the best idea, which is to collect the lymph nodes from rabbits with Masugi-nephrosis

Bradley How often?

Dock Say two or three times The lymph nodes would be those at a different level up in the neck, perhaps, or in the mediastinum One could use lymph nodes as a control, in the slaughtering of the beast

Bull There would be no urea, but inulin, perhaps

Miller It is difficult to visualize massive reabsorption of inulin in some of those nephrotic patients that Dr Lee Farr (36) studied, in whom the inulin clearance was supernormal?

Dock The PAH is supernormal, too, sometimes Certainly, not much is diffusing back at that state of the disease

Lauson Yes The two children in whom inulin was measured at three plasma levels had severe nephrotic syndrome The four childen who were given carinamide also had the nephrotic syndrome Most of the children in the large series in which creatinine/inulin, or thiosulfate/inulin clearances were measured had nephrotic syndrome, but a large fraction had acute or chronic glomerulonephritis

Pitts In relation to your first point, would that not be equally true of urea?

Lauson The ratio of urea to inulin clearances was measured throughout most of these experiments In the cases in which carinamide depressed C_{IAH}, the ratio of urea/inulin clearance remained unchanged Similarly, when plasma inulin concentration was varied, urea/inulin clearance was unaffected

Dock The urea clearance was low?

Lauson Yes In the inulin and carinamide experiments, the urea clearances were moderately to severely reduced

Dock Compared with their inulin clearance?

Lauson No Compared with normal children In these patients, there was nothing unusual about the ratio of urea/inulin clearance when related to the observed urine flow They were not like the very advanced nephritics who tend to have an urea/inulin clearance ratio approaching unity

Berliner That does not rule out the possibility of passive back diffusion

Lauson Of the total filtrate?

Berliner Yes, or some fraction of the filtrate Was that what you meant Dr Pitts?

Pitts Yes

Dock There is no conceivable way of testing for intrarenal extravasation of glomerular filtration, is there? In "ischemuric disease," the tubules lose their linings and presumably filtrate would just extravasate out into the interstitial substance of the kidney It is hopeless to try to work out any way of seeing how much inulin escapes into the interstitial substances of the kidney, when the tubules are permeable to inulin and everything else in the glomerular filtration rate

Berliner I suppose from a functional point of view we really do not care what happens to those factors that do not contribute to the final urine

Pitts It is just as though it had not been formed at all

Dock I believe Dr Oliver would think there was some difference between testing the function of a normal kidney, and one with a

talking, I wondered whether what I have to say might help to explain his findings, I should like to emphasize that these results are only preliminary

Figure 9 shows the concentration of potassium in the glomerular and tubular fluid as compared with that in serum, and it is quite obvious that at the glomerulus there is a concentration practically identical with that in serum The concentration drops off, and I think the lowest figure is about 20 per cent of that of serum I have used serum in most of these studies These points indicate a very dramatic reduction of potassium concentration ratio in the proximal tubule but I am not sure that all collections will show figures as low as this The curve may spread, giving ratios more like those shown at the right for the distal tubule Taking them as they stand, I think they seem to indicate a rather striking reduction of potassium in the proximal tubule, in fact, so much so that I cannot help wondering whether it means that potassium is being absorbed over the area of glucose reabsorption and whether it is necessary for potassium to be reabsorbed at the same time as is glucose As soon as I am a little more sure of the pattern, I should like to try some experiments on phlorhizinized animals

The 'K per inulin' ratios given below mean, of course, the potassium concentration ratios over the inulin concentration ratios Presumably this ratio for glomerular fluid over serum would be approximately one The first ratio shown at about 10 per cent proximal is 86, and they vary in the next group between 70 and 50 They then drop down to 30, and finally to the lowest of 08, near the end of the proximal tubule Each dot represents an individual experiment on a different animal, but where 'K per inulin' ratios are shown, inulin and potassium were determined on identical samples

Now, to proceed to the distal tubule some of the dots obviously are higher than the lowest shown for the proximal tubule, but still showing K per inulin' ratios near 30 A dot at about 70 per cent distal indicates a tubule fluid potassium concentration higher than that of serum and another dot at the end of this section a fluid potassium concentration about twice as high as that in serum

EDITOR'S NOTE Dr Bott wishes to add the following statements to her remarks at the conference

It may be of significance that in the animal showing the highest concentration ratio for potassium the serum potassium was only 2 1 mEq per L Potassium concentrations of bladder urines not collected simultaneously with any experiments indicate a fairly wide range for potassium content, some being less than 1mEq per L This may mean

Miller And yet, the defect, the tubular lesion, is presumably full blown

Dock In these patients, there is a different problem from that in the group Dr Bywaters and Dr Oliver have been studying Were these mercury lesions that the trypan was flowing out of?

Oliver No, they were spontaneous canine lesions in Bright's disease

Pitts I think before Dr Luetscher continues along more clinical lines, Dr Bott might describe her experiments on sodium and potassium excretion

Bott These remarks do not really belong in a more or less clinical discussion, but a few people have expressed interest in some work I have done on the *Necturus* kidney* When Dr Luetscher was

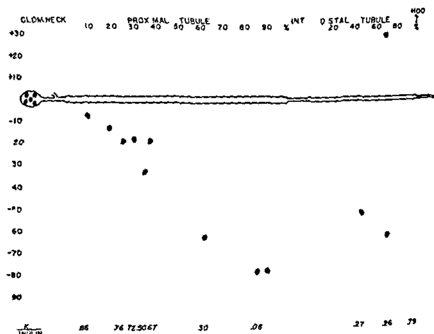


FIGURE 9 Shows preliminary figures for the kidney of *Necturus* Concentration of potassium in glomerular and tubule fluid as compared with that of serum is represented for individual experiments by black symbols Their positions relative to the tubule diagram indicate the section of the tubule from which the fluid was collected while their positions relative to the ordinate indicate the percentage by which the potassium concentration differs from that of serum For most of the experiments ratios for the potassium and inulin concentrations are given *below* the symbols for the corresponding collections

---

*This work is currently supported by a grant from the Life Insurance Medical Research Fund

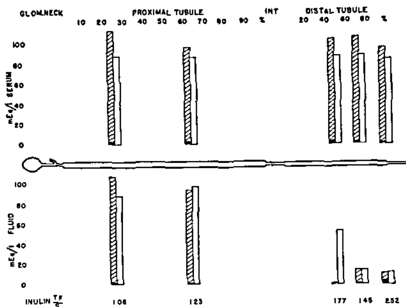


FIGURE 10 Gives preliminary figures for the kidney of *Necturus* Cross hatched bars indicate sodium black bars potassium and white bars chloride The constituents of serum are shown above the diagrammatic nephron those of tubule fluid for the same experiment are shown directly below and the inulin tubule fluid per serum concentration ratio for the pair is shown at the bottom The position of each pair of diagrams relative to the nephron diagram, indicates the section of the tubule from which the fluid was collected

tubule fluid electrolyte picture is only slightly different from that of the serum Next, at 64 per cent proximal, chloride has risen and sodium has stayed about the same as it is in the serum above It brings out a point that I tried to emphasize in the first meeting of this group, that I think this pattern is much like that in animals but perhaps not so extreme Over a large part of the proximal tubule, at least sodium seems to stay about the same in the tubular fluid as it is in serum, and the chloride seems to mount to balance the sodium, or sodium and potassium I believe that that same thing happens in the mammalian tubule Unfortunately, at the moment, I have no more figures between these and the ones for the distal tubule but there is no reason why, in this animal, we should not be able to get beyond this point in the proximal tubule, and collect enough fluid for this type of experiment

Now, to consider the distal unfortunately I lost a part of the

that not all distal tubule potassium concentration ratios will be in the range shown in Figure 9

Bott Even in this experiment the "K per inulin" ratio was still only 79 I am not sure that any of this means 'secretion' of potassium Possibly it could, but with the number of points we have so far, I think we cannot be sure If these were all on the same nephron of course, it might mean secretion, but we have to keep in mind that all are different animals and collections I have never had a ratio of potassium per inulin concentration higher than 1 up to this time They have always been lower than 1 If with more experiments the line definitely goes down, as it seems to in the proximal, and then goes up, as it seems to in the distal tubule, perhaps secretion will be shown Once the pattern is definitely established I hope to try 6063 *to see whether we can force any so-called secretion* This refers to the carbonic anhydrase inhibitor used by Berliner (37), and others, to decrease hydrogen ion and increase potassium excretion

Forster How did you prepare the animals? When you were working *with* normal *potassium levels, were you perfusing the* specimens, or were they pumping blood?

Bott No, these animals were anesthetized with urethane, and the head kept in dilute urethane Nothing had been administered except inulin subcutaneously, dissolved in water I tried not to disturb the electrolyte balance more than was necessary

Berliner You have not given potassium?

Bott I have not given it so far However, that is obviously another thing I wish to do

In Figure 10 are shown the results of a few experiments in which we have determined as many electrolytes as possible along with inulin Here we have not only the usual difficulty of determining the relation between the concentrations of constituents of tubule fluid as compared with plasma, but an attempt is being made to show at least something of the anion cation balance in the two fluids This puts much more strain on our analyses Milliequivalents of electrolyte per liter of serum are given above the nephron, and milliequivalents per liter of tubule fluid below the nephron The cross hatched bars indicate sodium, the black, potassium, and the white, chlorides The group of bars above the nephron show rather typical pictures for serum, although they are not all exactly the same Each serum diagram with its tubule fluid constitutes one experiment, the inulin concentration ratio for each experiment appearing at the bottom of the chart At 26 per cent proximal the

served before, and was even more pronounced in the mammalian experiments where chloride roughly balanced the sodium, in the only two cases in which sodium was determined (38,39)

Berliner Dr Bott, do you remember whether the pH measurements reported by Montgomery and Pierce (40) referred only to the frog or was *Necturus* also included?

Bott They did use *Necturus*

Berliner Your data would not appear to fit very well with the hypothesis that pH does not change in the proximal tubule

Bott Montgomery and Pierce observed no significant change in pH in the proximal tubule I am hoping to do some pH determinations along with these electrolytes

Berliner Your data would suggest a change of the order of a pH unit or more, if there were no appreciable amount of bicarbonate would they not?

Bott The carbon dioxide level could not fall in the fluid?

Berliner If these figures are correct, there is no appreciable amount of bicarbonate If we assume, as most people do, that the carbon dioxide tension has not changed markedly, the pH must have fallen considerably and not just a tenth or two of a unit

Bott Yes I believe that these figures would indicate a change

Berliner I suspect that the pH in the proximal tubule may vary with the circumstances

Bott I would not put too much stock in these preliminary experiments Possibly some of the questions under discussion are within total experimental error and we certainly need many more figures

Forster What do you do about the tubule s communication with the peritoneal fluid?

Bott We keep the pressure, against which we are collecting high enough to be sure we are not pulling in anything

Forster How do you think that opening functions normally, is it properly called the "nephrostome"?

Bott Yes

Forster Do you think the pressure is normally too high in the lumen of the tubule to allow any peritoneal fluid to enter the tubule?

Bott I do not know under what conditions it does function I agree that there is some chance of contamination although the kidney surface is comparatively dry and covered with oil during the experiment

Berliner These were all done with unmanipulated animals except for the actual puncture?

sample and was not able to determine sodium in the one at 50 per cent I put the rest of the figures in because I believe that probably the chloride roughly balances the sodium and potassium again, and then, as we proceed along the tubule, very small amounts of sodium and chloride are shown, the sum of the cations approximately balancing the anions The inulin TF/S figures increase from 1 06, for the early proximal collections, to 2 52 at the end of the distal tubule, which is a rather high ratio for *Necturus* These ratios indicate water reabsorption all along the nephron

TABLE I

Tubule Fluid per Serum Ratio

Site of Collection	Inulin	K	Na	Cl
Prox 20 per cent	–	–	94	–
Prox 26 per cent	1 06	61	96	1 01
Prox 64 per cent	1 23	37	1 00	1 13
Distal 50 per cent	1 77	48	(59)	61
Distal 70 per cent	–	1 29	16	–
Distal 74 per cent	1 45	37	11	17
Distal, end	2 52	2 00	08	15

Table I shows some of the same experiments, with a few scattered results added just to bring out certain points Notice that the inulin *concentration ratios increase gradually but not uniformly* because the animals and collections were different The potassium ratios drop in the proximal and then become higher again, in the distal tubule Three *sodium concentration ratios indicate that sodium remains* about the same as it is in the serum throughout at least a part of the proximal tubule For the distal tubule, the figure shown in parentheses is *estimated from the chloride and potassium* determinations and is not reliable, but rapidly falling ratios are shown for the end of the segment The figures show that these animals were in good condition *for reabsorbing sodium and chloride*, and, especially in the last one, for concentrating inulin The slight rise in chloride concentration ratio in the proximal tubule has been ob-

after treatment Exceptions to this rule exist A better correlation is found between diuresis and reduction of pre existing high output of sodium retaining corticoid in the urine

The ability to excrete sodium and water has been much easier to stimulate than the reduction in proteinuria (41) If we look at a series of patients who have been treated with ACTH, cortisone, or hydrocortisone (Figure 11), we find that most patients who

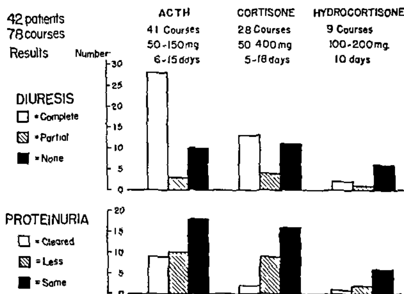


FIGURE 11 Immediate results of treatment of nephrosis Reprinted by permission, from Luetscher J A Jr, Deming Q B Johnson B B and Piel C F Advances in management of the nephrotic state *J A M A* **153**, *1236 (1953)*

receive a therapeutic dose of adrenocortical steroids respond with diuresis usually with complete elimination of edema, failure is observed in only about a third of the patients The somewhat poorer results which we obtained with cortisone, or with hydrocortisone, are due I believe, to suboptimal dosage or absorption of these materials while we were learning to use them If an adequate dose had been given the results in these columns would probably approach those which were observed with ACTH Proteinuria, on the other hand, seems more difficult to modify In only one quarter of the patients who were treated, the daily protein excretion diminished

Bott Yes, the animals were kept in as normal a condition as possible

Pitts Of course, ideally, you would like to have the sodium-potassium chloride figure for the study Can you obtain enough fluid to conduct all these experiments?

Bott Yes, I think so Of course we have to collect over a long period Many of the experiments require an hour, and there are difficulties in keeping the inulin level fairly steady, and the quartz needle in properly I must admit that I have attempted many more experiments over the past year than I have shown in these three diagrams They are not easy but they can be done, and with methods in which less material is needed, I certainly think we shall be able to do quite a few things on one sample If we eliminated inulin we could determine the electrolytes you mention, and also pH

Berliner Those of us who have been assuming, on the basis of slim experimental evidence and a great deal of inference, that most of the filtered potassium is reabsorbed in the proximal tubule, are very pleased to see these data

Pitts Dr Luetscher, will you now continue?

Luetscher The important physiological changes which are observed in these patients when they are treated with the adrenocortical hormones have been described earlier in the discussion Considerable difficulty in interpretation arises because so many things happen at once that we are not in a strong position in defining cause or effect Furthermore, the functional pattern is not the same in all patients before treatment, and the response to treatment is not uniform There is a striking difference in the ease with which we are able to modify the picture in different individuals It is an old story in the treatment of the nephrotic syndrome that there are some patients who seem to be quite ready to produce a diuresis under almost any stimulus, and there are other patients in whom it is very much more difficult to induce

With albumin, it seemed quite clear that those patients who responded best were those who had a minimal impairment of renal function In the patients who started with a reasonably good filtration rate, and those in whom a good expansion of filtration rate followed treatment, the probability of inducing diuresis was greatest (25)

In the nephrotic syndrome treated with the adrenocortical hormones, a similar pattern has been evident In general, the patients have responded best when renal function has been not too seriously affected, or when considerable improvement in function occurred

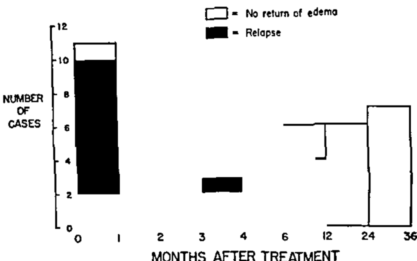


FIGURE 12 Duration of relief of edema in 26 patients after 44 brief courses of treatment Reprinted by permission from Luetscher J A Jr Deming Q B Johnson B B and Piel, C F Advances in management of the nephrotic state *J A M A* 153 *1236 (1953)*

remain free from edema as well as from other evidences of disease, if the remission lasts for more than one year

Figure 13 shows the current status of all patients one to three years after treatment Approximately 43 per cent of both adults and children were still in remission with normal clinical appearance clear urine and free of protein or any abnormality in sediment Renal function studies were not done at this time Possibly some chronic impairment might be found but these patients were stabilized in the pattern of normality as far as they were able to achieve it and as far as it was evident on clinical examination Continued evidence of disease was seen in those patients in whom a remission with reduction in proteinuria had not been established Abnormalities in the urine were associated in many instances with clinical edema A certain number of the patients found their way to the final column of death from intercurrent complications or *progression to chronic renal insufficiency*

In watching these patients over a period of time it is obvious that the clearing of the urine of protein is a very much more fundamental change one which is harder to achieve and yet once achieved is more likely to lead to a satisfactory end result The use

to a normal level The number of patients in whom proteinuria continued unchanged in spite of full therapeutic doses, is unfortunately large

Lawson May I ask whether most of the patients who did not show a decrease in proteinuria were in the group in which diuresis did not occur?

Luetscher Yes, the tendency for diuresis and an improvement in proteinuria to occur together is a very striking one, not only in terms of the patients, but also when we consider the time at which it appears The maximal reduction in proteinuria is usually observed at the time of diuresis regardless of whether it appears during the administration of hormone, or after
is easier to stimulate and I would
improvement, since we have not seen significant reduction in proteinuria without diuresis

There is apparently no obstacle to a complete elimination of edema even though proteinuria continues at the same rate and even though the serum proteins are little affected during the release of fluid I think therefore, that one does have to consider that these two ideals of treatment, i e , the ability to return to a more normal handling of electrolytes, and the reduction of protein in the urine, are achieved in different degrees, if not in different ways in patients who are treated with the adrenocortical steroids

The duration of improvement in diuresis or proteinuria is extremely variable Recurrences occur spontaneously in a large proportion of these patients and the stimulus to relapse is often ill defined A respiratory infection without detectable pathogens which are ordinarily associated with recurrent nephritis, such as the hemolytic streptococcus or the pneumococcus, is the most common precursor of relapse Almost any stress to the patient seems to be enough in certain instances In one case a moderate exposure to sunlight which produced only mild dermal erythema, was followed by recurrence of the whole nephrotic picture Certain allergens and drugs have been blamed for other relapses

The duration of relief of edema after treatment with the adrenocortical steroids is charted in Figure 12 Relapse is frequently observed within the first month after therapy, additional recurrences occurring less frequently in succeeding months The apparent increase in later months is artificial, being related to the scale in which we put two months and six months in the later periods respectively After a year of freedom from edema there is a tendency for the pattern of remission to become stabilized These patients

Where all this fits in with spontaneous adrenocortical activity, it is difficult to say The observation that remission was just as likely to occur after the cessation of therapy as during treatment with ACTH or cortisone, has confused us Certain patients who have shown no tendency to improvement during the treatment for as long as two or three weeks, may still show striking improvement when the hormonal therapy is withdrawn The association between diuresis and the improvement in proteinuria has been a very close one, and the improvement in proteinuria is as likely to occur some days after the end, as it is during the course, of treatment

We should be somewhat cautious in the interpretation of post-treatment changes, because one sees sometimes an increased excretion of adrenocortical steroids of certain types in the urine during the posttreatment phase Whether this is related to an improvement in renal function, or to diuresis which may produce an increased clearance of steroids, or whether it represents an alteration in secretion or metabolism of adrenocortical steroids, we are not in a position to state at the present time There is certainly much more to learn about how these agents act, and about the optimal methods of treatment The nephrotic syndrome has sometimes been con
en, but in adults it has
to chronic course and
en and adults has not
been obvious in our experience We have one patient of 50 years of age, for instance, who, as far as we can make out, has made a complete clinical recovery although she may still show some evidence of impairment of renal function The activity of the disease has not been in evidence for three years In the group as a whole, we have had the impression that there was no real difference in the outcome of our adult group and our children's group although a perusal of the literature would indicate that, untreated, there might have been quite a striking difference

Swan On what basis have you chosen patients for inclusion in this group?

Luetscher We have made no attempt to distinguish between so-called pure or lipoid nephrosis and those patients in whom evidence of the existence of hypertension or hematuria might have suggested a more inflammatory or glomerulonephritic component On the other hand, we have not treated patients who have been frankly azotemic or uremic at the time they came up for consideration We may have included a few patients with *lupus erythematosus*, in whom the diagnosis was not evident at the time they were treated,

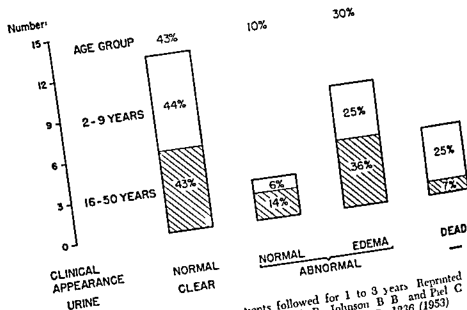


FIGURE 13 Present status of 30 patients followed for 1 to 3 years Reprinted by permission from Luetscher J A Jr Deming Q B, Johnson B B and Piel C F Advances in management of the nephrotic state J A M A 153, 1236 (1953)

of these adrenocortical agents simply as diuretics has little effect on the ultimate outcome of the disease From a clinical standpoint we have been impressed with the need for early and intensive treatment of these patients, with an eye to the production of a more complete and lasting remission

We have been using short courses of therapy These data are based almost entirely on treatment of patients for periods of ten days to two weeks There are cogent practical reasons for not using heavy, continuous therapy with the adrenocortical agents because of the expense and difficulty involved, and because of the added risk to the patient We have been reluctant to agree to the chronic administration of the steroids Yet I feel that these results may force our hand since the striking modification of the clinical pattern lasts only for short periods in many patients Although the nephrotic episode has been shortened in certain cases, others have not been helped very much by the use of these materials in brief courses In certain patients who show a tendency to relapse, we are probably going to have to continue administration of the materials in a more continuous fashion, in order to produce a long term modification of the disease

Oliver I think it would be very helpful if you would tell us your criteria for this group What are the characteristics of this nephrotic episode?

Luetscher The group was composed of patients who came to the hospital with an insidious onset of the disease They uniformly had no history of an acute episode with the classical manifestations of hemorrhagic nephritis but presented a story of weight gain of feeling tired and heavy and of swelling of the face or ankles Although some patients had a respiratory infection about the time of onset there was no concrete evidence that they had had a recent encounter with the hemolytic streptococcus either in the presence of increased circulating antistreptolysin or in cultures from the throat The clinical picture which they presented was that of a massive generalized edema The urine showed heavy albuminuria and generally an absence or a rarity of red blood cells although in a few instances the Addis count showed red cell excretion as high as 80 million per day The characteristic blood casts of hemorrhagic nephritis were uniformly absent The blood pressure was usually normal but a few patients showed a rather variable hypertension which generally subsided when they were put to bed They all had significant hypercholesteremia which is a very rare accompaniment of the acute episode and in my limited experience tends to fall with an acute exacerbation of a hemorrhagic nephritis in a patient who is passing through a degenerative stage of chronic

an

iod

of two weeks to a month before therapy was given there was no tendency for the abnormalities to subside spontaneously On the contrary edema tended to grow heavier and the disease to progress deeper into the pattern which we have already described

Oliver But do you believe that this syndrome can occur in an inflammatory subacute glomerulonephritis as a nephrotic episode?

Luetscher There has been no patient in our series who has shown a documented and clear-cut acute hemorrhagic nephritis progressing into this pattern

Oliver Have glomerular crescents been found in the kidneys of any of these patients?

Luetscher We have had patients who died and whose kidneys revealed glomerular crescents but they have uniformly not given us a history of an acute episode which was recognized clinically

Oliver Do you accept the crescents as evidence that there had

but we have attempted to exclude patients who clearly had some other disease leading to a pattern resembling the nephrotic syndrome

Bradley How many patients with hypertensive disease did you study?

Luetscher A relatively small proportion of the group had any significant hypertension and when this has been present, it has been usually rather labile and of low grade

Bradley In adults or children?

Luetscher Both

Berliner Are there any hypertensives among those patients who appear to have been cured?

Luetscher A trend toward hypertension of a mild degree is not apparently a serious factor in the prognosis of the nephrotic syndrome in our experience and as I read reports of other groups who have studied the progress of the disease, this does not seem to be a major factor On the other hand, a very striking and symptomatic hypertension is certainly an unfortunate prognostic index

Bradley Is it possible that some of the adults may have suffered from acute nephritis?

Fishberg Before the days of ACTH, recoveries were not too rare in adults Those of you who are acquainted with the publications of Albert Epstein (42 43) who, I think, treated more of these cases than anybody else, remember that he used to stress that a not inconsiderable fraction of them improved which he attributed to the high protein diet I have seen one patient get well after ten years of proteinuria and during those years the disease was continuous I have seen another patient who lasted several years But I am confident of one thing among the cases seen by Dr Epstein and a good many others which I had seen before the days of ACTH there was nothing like a 45 per cent recovery rate in adults As a matter of fact they were so exceptional that we used to demonstrate them whenever we had such a case

Luetscher Perhaps we have been fortunate in the group that we studied As far as the exclusion of the patient with acute nephritis goes if you mean a classical acute glomerulonephritis, I believe that we can usually make a clear distinction between those two groups

Oliver How about the subacute cases?

Luetscher If you mean the type of nephrotic syndrome which is preceded by a definite acute hemorrhagic nephritis, there are no such patients within this group

to die of intercurrent infection, at the present time deaths from infection have been uncommon As a matter of fact, we have been very fortunate in not having any deaths from intercurrent infection in the group that we have been following, which is primarily a tribute to the clinicians who have been taking care of these patients, and who have provided prompt and effective treatment

Burnett I assume that those who died did so because of renal insufficiency? Did they have edema when they died?

Luetscher Most of these patients were edematous up to the time of their death, but with progressive evidences of renal insufficiency Occasionally the terminal illness began abruptly just a week or two before death, with rapid rise in blood pressure, and acute deterioration of renal function

Dock In your group of patients, did about half of the remissions occur while therapy was still being given, and the other half after it had been discontinued?

Luetscher Yes, and in a few instances, which help to keep us honest and humble, the remission occurred spontaneously in the patient after we had done our best with the hormone and failed

Dock You mean more than three weeks after discontinuing it?

Luetscher Yes We had one patient, for example, who was totally resistant to all the treatment that we gave him at fairly high dosage levels, and who then, in the midst of an acute illness from chicken pox and pneumonia, had a pronounced diuresis, six months after his last course of adrenocortical hormone

Merrill Dr Luetscher, will you elaborate a bit on the long term therapy which is used in the case of these patients? How long do you continue it, and what indications are there that the ultimate prognosis will be improved thereby?

Luetscher We have no reliable data as yet, they take years to accumulate The problems we encounter are as follows If we try gradually to discontinue the dose of hormone, we are likely to see a recurrence just as though we had stopped giving hormone If we continue at a high dosage over a period of months, the incidence of complications becomes very large One compromise which may be advantageous in long term therapy has been high dose, intermittent treatment, in which a patient receives heavy doses of the adrenocortical steroids for three or four successive days out of each week (44)

Dock Did your studies of the sodium-retaining principle in the urine give you any evidence that there was a pause in adrenal function after you discontinued cortisone?

been a tissue reaction in the glomeruli that is usually called subacute glomerulonephritis?

Luetscher At the end, they had changes in their glomeruli which were indistinguishable from those of glomerulonephritis, but we wondered whether these changes might have developed under our eyes as we observed the later development of hematuria, hypertension and renal insufficiency after months or years of the nephrotic syndrome When a patient dies from some intercurrent event in the early stages of the nephrotic syndrome, there are often minimal changes in the glomeruli, which resemble in some ways the lesion which Dr Carolyn Forman Piel (2) has shown us in rats sacrificed within a few days after nephrotoxic serum was administered, where there was predominance of basement membrane thickening or exudation They have not shown the changes which I would have associated with a subacute glomerulonephritis Those who died later in the disease with a picture of chronic renal insufficiency have shown, as Drs Piel and Ehrich (2) pointed out, extensive glomerular lesions with scarring, obliteration, hyalinization or crescent formation, all of which are changes we would associate with a chronic and progressive glomerulonephritis The feeling in our group has been that the pattern of the reaction has changed in these individuals, but we could settle that point only by serial biopsies beginning at an early stage, rather than waiting for postmortem observation

Berliner Among these patients were there any who were known to have had albuminuria without other symptoms for any considerable period before the onset of this syndrome?

Luetscher Yes, there are occasional patients who have been known to have proteinuria before the onset of the clinical picture On the other hand there are others who have been examined very briefly before they came under observation, and they have been found to have a clear urine at that time

Swan Dr Luetscher, would it be possible to assemble data for a similar group of adults seen at your hospital with this same disease prior to five or six years ago?

Luetscher We have not been able to do so The elimination of intercurrent infection as a major cause of death has changed the course and duration of the nephrotic syndrome in recent years The general use of effective antibiotics at just about the same time as the adrenocortical steroids became available, has made it difficult to compare the present results with previously published series Whereas in previous studies about one third of the patients used

should ascribe to an improved level of circulating protein and possibly to some accumulation of extracellular fluid at that time General circulatory improvement may be at work, as well as any influences on the regulation of the renal circulation which may arise at that time

Berliner The effect of cortisone on filtration rate in the dogs is not dependent upon the retention of sodium I do not know whether that is true in man In the dog we obtain increases in filtration rate, even though the animal goes into negative sodium balance This has been reported by Davis and Howell (47)

Burnett Is it greater than when the dog is receiving large quantities of salt?

Berliner It is about the same order of magnitude

Merrill We have found that in the ones receiving large doses of cortisone no increase in filtration rate has been observed when sodium is restricted I think the root of the problem is that one can see a decrease in proteinuria with increasing filtration rate following the administration of ACTH and cortisone

Lauson A great deal can be gained by applying the clearance concept to the problems of proteinuria (23) Other things remaining constant, an increase in GFR ought to result in an increased clearance of albumin An increase in the plasma concentration of albumin at a time that albumin excretion remains unchanged, or falls indicates a diminished albumin clearance We like to use the ratio of albumin clearance to GFR (as measured by the inulin clearance or, less adequately, by the endogenous creatinine clearance) as a rough index of glomerular permeability to albumin relative to the permeability to water Both the plasma water and albumin are exposed to the same capillary surface and to the same hydrostatic pressures in the glomeruli, although of course, albumin restrains the outward movement of water but does not restrain its own movement Therefore, quantitative changes in relative permeability can be crudely estimated by changes in this clearance ratio I meant to comment on this earlier in connection with Dr Luetscher s Figure 11, which showed that quite a number of patients exhibited little or no decrease in proteinuria after ACTH or cortisone therapy I feel sure that most of these patients would have shown a decrease in albumin clearance because plasma albumin usually increases somewhat, and more important they would have shown a decrease in the ratio of albumin clearance to GFR, because of the decrease in albumin clearance and [illegible] in GFR

Luetscher The urine is the wrong place to study steroid levels because of the changes of renal function which occur with the diuresis Marks (45), Galan (46) and others, have pointed out the tendency for increased excretion of steroid associated with increased renal function and urine flow We can only say that the maximal excretion of 17-ketosteroids, and of certain urine corticoid fractions, may continue after the end of therapy and through diuresis in some patients On the other hand, the excretion of other steroids tends to fall off The variation in pattern in different patients and in different fractions, makes it *difficult to define accurately the pattern* of steroid excretion during the posttreatment phase Even this will not give us a final answer until we can follow blood levels of the major components

Dock You would expect the glomerular filtration rate to be rising when the adrenal function was suspended, though, would you not? It would tend to go in the opposite direction I gather

Luetscher The rise of creatinine clearance is maximal at about the end of therapy and tends to be sustained for some days after that It may continue to increase slowly if a remission begins Diuresis may occur with either a rising or a falling creatinine clearance after the end of therapy

One can increase the glomerular filtration rate of a normal man, as Dr Burnett has shown us, by the administration of ACTH or cortisone Improvement in circulating albumin levels occurs in patients so treated, and this could raise the filtration rate of a patient with a nephrotic syndrome just as in the case of the administration of albumin Any change in the underlying disease picture which may occur at that time may be another contributing factor Again, we are dealing with a complex situation

Burnett I wonder if the mechanisms are not a little different Subsequent experience has shown that the increase that we initially demonstrated was probably largely related to the expansion of extracellular volume All the original subjects were getting a good deal of salt One certainly minimizes, or perhaps even removes the effect on filtration rate in the normal individual, if salt is restricted

Luetscher I am sure that is an important point On the other hand, the changes might reflect an increase in plasma volume As you know the nephrotic is usually laboring under the difficulty of a low plasma volume, and there is certainly an improvement in protein levels in a number of these patients while they are under treatment Barnett has pointed out that a number of these patients may also show increased plasma volume during therapy, which we

Bradley Why does the albumin output decrease as a result of treatment with ACTH?

Lauson In philosophical terms, we thought that ACTH or cortisone would bring about a reversal toward normal of the glomerular lesions (23) This favorable trend is indicated by the rise in GFR, if it had been depressed, and by the reduction in protein or albumin clearance If, after repeated trials to achieve these results, such therapy fails, this fact may have prognostic meaning It seems reasonable to assume, after repeated failures, that many glomeruli are irreversibly scarred On the other hand, if it is possible to induce a substantial increase in GFR and a decrease in albumin clearance, even though the disease has been present for years, it gives one the hope that the glomerular lesions may yet heal

Bull As Dr Luetscher has said, we have all had the humbling experience of treating a person who has not responded, and yet a short while later, spontaneous improvement occurs

Lauson Yes, this happens often enough, that is why I said repeated trials should be made Riley (48), at the Babies' Hospital in New York, has had a number of patients in whom as many as three courses failed to induce diuresis, but in whom another course was successful

Swan Dr Lauson, on what basis can you assume that the reabsorption of protein by the tubule does not change?

Lauson I do not suppose there is any way to prove this assumption I know too little about the results of renal biopsy to guess whether, after successful treatment with ACTH or cortisone, the tubules would show so few lipids and proteins in their cells that it would indicate reabsorption had improved

Bull I am not arguing that increased protein reabsorption is responsible for any of this improvement, but I think it is possible that the tubules could reabsorb a lot of protein On considerations of both size and electrical charge, albumin is likely to be filtered more readily than globulin, or at least to the same extent as globulin and yet in postural proteinuria we sometimes find more globulin than albumin in the urine This suggests that albumin is being reabsorbed If we accept this, and make a further assumption that globulin is not reabsorbed, we can use globulin as the indicator of albumin filtration and make the usual reabsorptive Tm type of calculation of the amount of albumin reabsorbed This would give a minimum figure for albumin reabsorption as it is likely that some globulin is reabsorbed also Using this type of calculation on specimens of urine from subjects with postural proteinuria I have seen

ratios in various parts of the tubule, and to establish whether significant protein reabsorption occurs

Bott Has it ever been proved quantitatively that protein is absorbed in any amount? I know that there are these histological pictures and so on Perhaps some of you remember the series of perfusion experiments that Dr Richards and I ran on *Necturi* and frogs (51), I hesitate to use them as arguments because I know that I myself would criticize one of the conclusions that we made The experiments were not designed to test whether or not there was reabsorption of protein, they were an attempt to find out something about the permeability of the glomerular membranes to larger molecules, and what influenced it

We did perfusions with proteins of various sizes, and the general conclusion was that it was largely a matter of size of the protein molecule, however, for proteins of about the same molecular weight, we did find differences We did not know whether it was a matter of shape, but we thought it could not be a matter of charge because proteins which had the same charge, as nearly as we could ascertain, showed differences in their passage through the membranes I am thinking of egg albumin and lactoglobulin Then we ran some indirect experiments on frogs in which we perfused inulin and proteins, and from the amounts of these in the urine calculated back to what the percentage filtration of proteins would be In these we obtained results similar to those for the direct experiments on *Necturi* and therefore our conclusion was that there could not have been very much reabsorption of protein

I think we should take the same animal and have collections made from the ureter at the same time as punctures are being made Perhaps more could be learned from this I realize that perhaps the leakage of protein in these cases is not up to the concentration that we were using, so that, percentagewise, we should perhaps have a larger amount of protein going back by some sort of reabsorptive or adsorptive mechanism But I think more quantitative work should be done on it before we attempt to draw any conclusions

Oliver What is one to say of preparations from animals into which we have introduced a protein-like hemoglobin which may

filtered If we look at kidney tubules we can see the cells of the proximal convolution filled with diffuse — I am not talking about droplets but diffuse — hemoglobin We can inject egg white and

was a pretty clear relationship between the blood level and the appearance of a fraction in the urine which made us feel that there was probably a minimal tubular component

Dock Perhaps the reabsorptive capacity was working maximally all the time If the reabsorption were at a constant level and were maximal it might give us the same results as if tubular reabsorption were minimal

Luetscher At some point we should find ourselves in a situation where the excretion would fall off sharply as the filtration rate fell

Bradley Studies of urinary protein output relative to filtration before and after assumption of the upright position have been made in our laboratory by Drs Willoughby Lathem and James Nickel* In some 20 patients with proteinuria with renal disease of various kinds the protein output *always fell in proportion to* the fall in filtration rate but the fall in filtration rate was associated with an equal fall in glucose Tm Apparently orthostasis evokes a renal vasoconstrictive response that affects the glomerular population in a random manner The concentration of protein in the urine increases Hence orthostatic proteinuria in this situation is solely a function of urinary protein concentration and is not a function of protein output

Berliner How long were your patients in the upright position?

Bradley From 30 to 60 minutes

Dock It is very striking when we study the proteinuria of rats with diminished kidneys that the less kidney we leave in and the greater the hypertrophy of the remaining unit the more severe the proteinuria is and the less the rat is able to get along without salt They do not become edematous so their synthetic machinery must be much better than ours However they get uremic and their proteinuria becomes more severe with recovery The proteinuria becomes very severe indeed Their urine volume is large and their daily output of salt and protein is high but the rat seems to be able to replace this protein in some fashion They are really marvelous in keeping their serum protein up with these tremendous levels of proteinuria

Luetscher It seems that we are in the same dilemma in separating glomerular from tubular effects on protein as we are when we study electrolyte excretion As Dr Oliver has reminded us all we can measure is what comes out in the urine I suppose Dr Bott will have to study nephrotoxic *Necturi* to determine the protein multi

*Unpublished data

like albumin? It is much better to tag the albumin and study that, which will eliminate a good deal of trouble

Bott There is a question of whether we can get enough through

Oliver We do not need to tag it

Dock How do we know that it will act in the same way as albumin?

Oliver As soon as we tag a protein, it is not protein, but a protein plus something else One can work with fluorescent antibodies where protein is not tagged, and yet the natural protein can be demonstrated quite specifically inside tubule cells, in bovine albumin, for example

Berliner But, as you said, that information indicates only how much is in the cells, and not the amount traversing them

Dock What I mean is, if we put Evans blue on albumin, the rat's proteinuria is not affected It will put out the same number of milligrams of protein with the dye on it as it did without the dye The color of the urine has changed, but the proteinuria has not

Oliver But the nature of the substance has changed It is no longer protein but protein plus Evans blue

Dock Yes, but the same amount of protein is excreted in the urine, so there is no change in terms of an ability to pass through the kidney If the rat has a severe proteinuria, the tubule cells are really bright blue We can take a rat's plasma, and dialyze it as long as we wish but we obtain no color at all in the dialyzed fluid We could put infinitely small amounts of radioactive chromate on albumin, and follow this in the tubules in animals, or even in men We can do biopsies, make an examination with radioautographs and learn a good deal about what is happening to the albumin which has had an insignificant change in its structure Experiments that can be carried out with hemoglobin can also be done with serum albumin that has an appropriate tag on it, and I am sure the differences between that and ordinary albumin are less than in the case of hemoglobin

Bott I was not studying hemoglobin to see how typical proteins behaved I was encouraged to undertake this study during the war by those who were interested in the 'crush syndrome" I am still dabbling in it, but I think that the hemoglobin story may be different from that of other proteins I agree that if enough albumin gets through the membranes to analyze it accurately, or if we could label it in some way as not to change it, serum albumin should be studied

Dock In electrophoresis, we cannot tell that it has been altered,

obtain a strong Millon's reaction diffusely distributed in the renal cells of the proximal convolution, or inject bovine albumin and demonstrate its presence in the tubule cell of the proximal convolution with fluorescent antibody

Pitts Dr Oliver, do you know what the effect of ACTH or cortisone is on the degree of proteinuria in these preparations, and on the appearance of protein in the tubules?

Oliver No, I do not know Only normal animals have been examined It seems to me that one cannot deny that these cells have *filled* up with a certain amount of absorbed protein One might say, "They have filled up and that is the end of it, they are not passing it on, and therefore it is not a functional reabsorption"

Bott Well, is that not in itself a point?

Oliver But if we do assume that, since you can keep these experiments going for long periods by repeated injections, there would seem to be some limit to the accumulation of protein in the tubule cells There apparently is not, because there is strong evidence (52) that the tubules of the rat absorb the albumin from the glomerular filtrate during the entire life of the rodent There is almost as strong evidence that the same continuous absorption of albumin occurs in man (53) I can think of the cells taking up protein to a certain amount, but there must be a point at which something of necessity happens the protein must be passed on, or metabolized in the cells, or both

Bott I have tried some experiments with hemoglobin, and I hesitate to mention them because results are erratic I still have not straightened out the difficulties completely I think hemoglobin has certain characteristics that none of the other proteins have, and certainly, for its size, it does come through the membrane remarkably easily Of course, we may say it is because it is made up of two small disks put together they may come apart, or it may be that because of their shape they can get through more easily I have tried some experiments in which I have actually taken samples from the ureter and the glomerulus at the same time, and I must say that in the case of the hemoglobin, sometimes the urine showed a *higher* concentration and sometimes the glomerular fluid Possibly this is a case of heterogeneity of nephrons, but I myself am confused about it As far as the other proteins are concerned, I have not tried, in the same animal, to take samples simultaneously from glomerular capsule and ureter, and I think it should be done

Dock Is it not a mistake to use hemoglobin in studying proteins

14 SIMPSON S A and TAIT J F Physico-chemical methods of detection of a previously unidentified adrenal hormone *Memoirs of the Soc for Endocrinol Memoir No 2* London Pitman Press 1953

15 BUSH I E Methods of paper chromatography of steroids applicable to the study of steroids in mammalian blood and tissues *Biochem J 50 370 (1952)*

16 LUETSCHER J A JR and JOHNSON B B Chromatographic separation of the sodium retaining corticoid from the urine of children with nephrosis compared with observations on normal children *J Clin Investigation* 33 *276 (1954)*

17 MATTOX V R MASON H L and ALBERT A Isolation of a sodium retaining substance from beef adrenal extract *Proc Staff Meet Mayo Clin* 28 *56) (1953)*

18 KNAUFF R E NIELSON E D and HAINES W J Studies on a mineralocorticoid from hog adrenal extract *J Am Chem Soc 75 4868 (1953)*

19 SIMPSON S A TAIT J F and BUSH I E Secretion of a salt retaining hormone by the mammalian adrenal cortex *Lancet* 2 *22((1952)*

20 FARRELL G L and RICHARDS J B Isolation of a potent sodium retaining substance from adrenal venous blood of the dog *Proc So Exper Biol* & *Med* 83 628 *(1953)*

21 HIRSCHMANN H HIRSCHMANN F B and FARRELL G L Partial synthesis of 16a 21 dia etoxy progesterone *J Am Chem Soc* 75 *4862 (1953)*

22 FAHR T Zur Frage der Nephrose *Ztschr f klin Med* 134 *533 (1938)*

23 BARNETT H L FORMAN C W and LAUSON H D The nephrotic syndrome in children *Advances Ped at 5 53 (1952)*

24 THOMPSON D D and PITTS R F Effects of alterations of renal arterial pressure on sodium and water excretion *Am J Physiol* 168 *490 (1952)*

25 LUETSCHER J A JR HALL A D and KREMER V L Treatment of nephrosis with concentrated human serum albumin II Effects on renal function and on excretion of water and some electrolytes *J Clin Investigation 29 896 (1950)*

26 LAUSON H D and THOMPSON D D Effects of decrease in glomerular filtration rate on cation excretion during loading with nonreabsorbable anions *Federation Proc* 12 *83 (1953)*

27 BURNETT C H The actions of ACTH and cortisone on renal function in man *Renal Function* S E Bradley Editor Trans Second Conf New York Josiah Macy Jr Foundation 1950 (p 111)

28 INGBAR S H KASS E H BURNETT C H RELMAN A S BURROWS B A and SISSON J H The effects of ACTH and cortisone on the renal tubular transport of uric acid phosphorus and electrolytes in patients with normal renal adrenal function *J Lab & Clin Med* 38 [illegible] *[illegible]951)*

it is just the same Its behavior in every other way is like that of natural albumin The hemoglobin will not act in the same as albumin in electrophoresis But whether or not chromate were added, tagged albumin would behave in just the same way

REFERENCES

1 OLIVER, J Essay toward dynamic morphology of mammalian nephron *Am J Med* 9, 88 (1950)

2 EHRICH, W E, FORMAN, C W, and SEIFER, J Diffuse glomerular nephritis and lipid nephrosis, correlation of clinical morphological and experimental observations *Arch Path* 54, 463 (1952)

3 PRESSMAN, D HILL R F, and FOOTE F W The zone of localization of anti mouse kidney serum as determined by radio autographs *Science* 109, 65 (1949)

4 LUETSCHER, J A, JR, and DEMING Q B Bioassay of sodium retaining corticoids and some changes in excretion of these sub stances in disease *Renal Function* S E Bradley, Editor Trans Second Conf New York, Josiah Macy, Jr Foundation, 1950

5 MCCALL M F and SINGER, B Studies in nephrosis chemical corticoids salt retaining factor, and effect of ACTH *J Clin Endocrinol* 13, 1157 (1953)

6 CHART, J J, and SHIPLEY, E G The mechanism of sodium retention in cirrhosis of the liver *J Clin Investigation* 32, 560 (1953)

7 CHART J J SHIPLEY E G and GORDON, E S Evidence for a sodium retaining factor in toxemia of pregnancy *Proc Soc Exper Biol & Med* 78, 244 (1951)

8 SINGER, B and WENER, J Excretion of sodium retaining sub stances in patients with congestive heart failure *Am Heart J* 45, 795 (1953)

9 JOHNSON B B Bioassay of adrenal cortical steroids on the basis of electrolyte excretion by rats effects of 11 desoxy and 11 oxy steroids *Endocrinology* 54, 196 (1954)

10 LUETSCHER J A JR and DEMING, Q B Treatment of nephrosis with cortisone *J Clin Investigation* 29, 1576 (1950)

11 LUETSCHER, J A JR, DEMING Q B, and JOHNSON B B Treatment of nephrosis with pituitary adrenocorticotrophin *J Clin Investigation* 30, 1530 (1951)

12 BARNETT, H L, FORMAN C W, MCNAMARA, H, MCCRORY, W W, RAPAPORT M, MICHIE, A J, and BARBERO, G Effect of adrenocorticotrophic hormone on children with nephrotic syndrome II Physiologic observations on discrete kidney func tions and plasma volume *J Clin Investigation* 30, 227 (1951)

13 BURTON R B, ZAFFARONI A, and KEUTMANN, E H Paper chromatography of steroids, corticosteroids and related com pounds *J Biol Chem* 188, 763 (1951)

43 ——— Nature and treatment of chronic nephrosis *ibid* 163, *167 (1922)*
44 LANGE, K, SLOBODY, L, and STRANG, R Treatment of nephrotic syndrome
Proc Soc Exp
45 MARKS, L J,
biologically acti
filtration rate *J*
46 GALAN, E, PEREZ STABLE, M, GARCIA FAEZ, O, UNANUE, E, GARCIA, O, LABOURDETTE, J M, and ALFONSO G Corticosteroids and antidiuretic substance in nephrotic children *Pediatrics* 12, *233 (1953)*
47 DAVIS, J O, and HOWELL, D S Comparative effect of ACTH cortisone and DCA on renal function, electrolyte excretion and water exchange in normal dogs *Endocrinology* 52, *245 (1953)*
48 RILEY, C M Nephrotic syndrome, effect of adrenocorticotrophic hormone *Pediatrics* 7, *457 (1951)*
49 PAPPENHEIMER, J R Passage of molecules through capillary walls *Physiol Rev* 33, *387 (1953)*
50 RYTAND D A, RANTZ, L A, and RANDALL, E Antistreptolysin O in urine and serum of patients with the nephrotic syndrome *J Clin Investigation* 29, *843 (1950)*
51 BOTT, P A, and RICHARDS, A N The passage of protein molecules through the glomerular membranes *J Biol Chem* 141, *291 (1941)*
52 SELLERS A L, ROBERTS, S, RASK, I, SMITH, S, MARMORSTON, J and GOODMAN H C An electrophoretic study of urinary protein in the rat *J Exper Med* 95, *465 (1952)*
53 RIGAS D A, and HELLER, C G The amount and nature of urinary proteins in normal human subjects *J Clin Investigation* 30, *853 (1951)*

29 BERGLUND, H, and FRISK, A R Further observations on mode of protein elimination, particularly of induced variations in proteinuria *Acta med scandinav* 96, 255 (1938)

30 CHINARD, F P, LAUSON, H D, EDER, H A, GREIF, R L, and HILLER, A A study of the mechanism of proteinuria in patients with the nephrotic syndrome *J Clin Investigation* 33, 621 (1954) (Supplement on the Nephrotic Syndrome)

31 MILLER, B F, LEAF, A, MAMBY, A R, and MILLER, Z Validity of the endogenous creatinine clearance as a measure of glomerular filtration rate in the diseased human kidney *J Clin Investigation* 31, 309 (1952)

32 MATTAR, G, BARNETT, H L, MCNAMARA, H, and LAUSON, H D Measurement of glomerular filtration rate in children with kidney disease *J Clin Investigation* 31, 938 (1952)

33 REDISH, J WEST, J R WHITEHEAD B W, and CHASIS, H Abnormal renal tubular back diffusion following anuria *J Clin Investigation* 26, 1043 (1947)

34 MATTAR, G, BARNETT, H L, MCNAMARA H, and LAUSON, H D Measurement of glomerular filtration rate in children with kidney disease *J Clin Investigation* 31, 938 (1952)

35 OLIVER, J BLOOM, F, and MACDOWELL, M Structural and functional transformations in the tubular epithelium of the dog s kidney in chronic Bright s disease and their relation to mechanisms of renal compensation and failure *J Exper Med* 73, 141 (1941)

36 EMERSON K, JR FUTCHER, P H, and FARR L E The relation of high and low urea clearances to the inulin and creatinine clearances in children with the nephrotic syndrome *J Clin Investigation* 20, 361 (1941)

37 BERLINER R W KENNEDY, T J, JR, and ORLOFF, J Relationship between acidification of the urine and potassium metabolism, *effect of carbonic anhydrase inhibition on potassium excretion* *Am J Med* 11, 274 (1951)

38 WALKER A M HUDSON, C L, FINDLEY, T, JR, and RICHARDS, A N *The total molecular concentration* and the chloride concentration of fluid from different segments of the renal tubule of Amphibia the site of chloride reabsorption *Am J Physiol* 118, 121 (1937)

39 WALKER A M BOTT, P A, OLIVER J, and MACDOWELL, M C The collection and analysis of fluid from single nephrons *of the mammalian kidney* *Am J Physiol* 134, 580 (1941)

40 MONTGOMERY H and PIERCE, J A *The site of acidification* of the urine within the renal tubule in Amphibia *Am J Physiol* 118, 144 (1937)

41 LUETSCHER J A JR, DEMING Q B, JOHNSON, B B, and PIEL C F Advances in management of the nephrotic state *J A M A* 153, 1236 (1953)

42 EPSTEIN, A A Concerning the causation of edema in chronic parenchymatous nephritis method for its alleviation *Am J Med Sc* 154, 638 (1917)

I think we should ask ourselves if it is worth while to attempt clinical transplantation at the experimental level or if we should wait until the problem is completely solved in dogs, or other animals? Some people have felt that we should wait Transplantation of the human kidney has never been attempted systematically before Antibodies to kidney tissue are presumed to be circulating in the blood of patients with glomerulonephritis These antibodies might be expected to exert an additional destructive effect against a transplanted kidney Instead of a transplant lasting five days, as in the animal we thought it might last half a day, or a day, in patients with Bright's disease

We therefore had a strong desire to learn the natural history of the human transplant We could then decide whether we should go back to the laboratory We also wished to know if the human arteries and veins would hold together, and whether the ureter remained nourished, because if one succeeded in transplanting the kidney, and the ureter sloughed right back to the renal pelvis then the problem would be centered around the ureter rather than the transplantation of the kidney

We had in mind making from six to ten human transplants and then reviewing the situation However, the results were so much

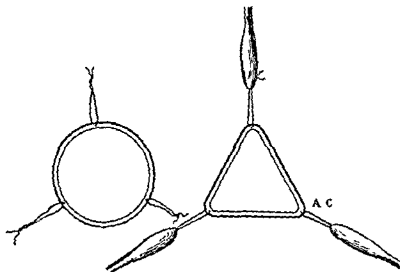


FIGURE 14 A diagram of Dr Carrel's method of suturing blood vessels Reprinted by permission from Carrel A La technique opératoire des anastomoses vasculaires et la transplantation des viscères *Lyon med* 98, 859 (1902)

THE PROBLEM OF KIDNEY TRANSPLANTATION

BENJAMIN F. MILLER
Department of Medicine
Harvard Medical School
and Peter Bent Brigham Hospital

For fifty years, attempts have been made to produce successful homotransplantation of animal kidneys The recent studies by W J Dempster (1), in England, and M Simonsen (2,3), in Copenhagen, both beautiful pieces of work, have shown that the dog homotransplant lasts, on the average, for four or five days, whereas we have been fortunate in having one clinical transplant that has functioned up to five-and-a-half months, and several others that have done considerably better than the best results in animals

The definitions in the field are relatively simple The "homologous" transplant, or the "homotransplant," is from one individual in the species to another, the "autologous," or the "autotransplant," is from one site in the same individual body to another site, the "heterologous," or the "heterotransplant," means from one species to another The words, "recipient" and "host," are used interchangeably for the animal, or the patient, who receives the donated organ

I have a strong emotional interest in transplantation, having seen so many young people, between the ages of 10 and 30, die of uremia I have tried to assess the magnitude of the problem of chronic uremia Suppose we were able to perfect the operation so that a human kidney which would function for an appreciable length of time could be transplanted. how many people would be benefited by such a procedure?

It is extremely difficult to obtain accurate statistics on renal disease They are mixed in with cardiovascular dysfunctions, "strokes," and heart disease, so the approximation is, I imagine, plus or minus 50 per cent, or even more But I think there are about a million deaths each year, throughout the world, of what one might call "salvageable uremia," that is, of patients whose original disease has burned out, or who have a condition like polycystic disease that affects only the kidneys If we could put back a workable kidney, these people would have their lives made a little happier, and perhaps they might even live out a normal life span

I think we should ask ourselves if it is worth while to attempt clinical transplantation at the experimental level or if we should wait until the problem is completely solved in dogs, *or other* animals? Some people have felt that we should wait Transplantation of the human kidney has never been attempted systematically before Antibodies to kidney tissue are presumed to be circulating in the blood of patients with glomerulonephritis These antibodies might be expected to exert an additional destructive effect against a transplanted kidney Instead of a transplant lasting five days as in the animal we thought it might last half a day, or a day, in patients with Bright's disease

We therefore had a strong desire to learn the natural history of the human transplant We could then decide whether we should go back to the laboratory We also wished to know if the human arteries and veins would hold together, and whether the ureter remained nourished, because if one succeeded in transplanting the kidney, and the ureter sloughed right back to the renal pelvis, then the problem would be centered around the ureter rather than the transplantation of the kidney

We had in mind making from six to ten human transplants, and then reviewing the situation However the results were so much

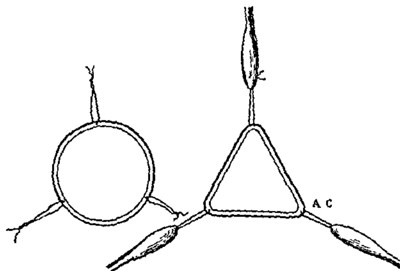


FIGURE 14 A diagram of Dr Carrel's method of suturing blood vessels Reprinted by permission from Carrel, A La technique opératoire des anastomoses vasculaires et la transplantation des visceres *Lyon med* 98, 859 (1902)

better than we expected that I think we now have justification for going ahead with additional studies at the clinical level

Let me acquaint you briefly with the background of the animal experimentation, which goes back almost fifty years Figure 14 is taken from Alexis Carrel's paper of 1902 (4), showing his technique for suturing blood vessels

In Figure 15 you can see the way it was actually carried out by this tridimensional procedure Once he was certain that he could suture arteries and veins in the dog and the cat he proceeded to a study of various transplantations with emphasis on the kidney

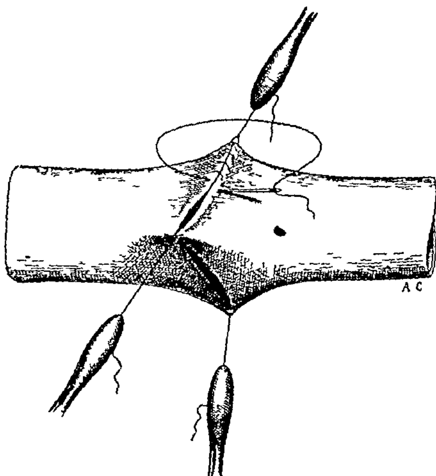


FIGURE 15 A further illustration of Dr Alexis Carrel's method of suturing blood vessels. Reprinted by permission from Carrel A La technique opératoire des anastomoses vasculaires et la transplantation des visceres *Lyon méd* 98, 859 (1902)

He transplanted kidneys in the cat and in the dog, paying very little attention to the functional results It is difficult, from the protocols, to know what was done beyond the very expert surgical procedure However, by 1907, Carrel (5) had performed a sufficient number of experiments in animals so that he felt there was no problem remaining in human transplantation – except to find donors! He states that he did not know where he could obtain a kidney to give a patient

Unfortunately, he did not realize the tremendous difference that exists between homologous and autologous transplants When C S Williamson (6), in the period from 1922 to 1926, conducted controlled experiments, it was immediately apparent that homologous transplantations in the dog failed very rapidly, whereas the autologous transplants made by precisely the same techniques functioned for months and even years The reaction in the homologous transplant is extremely rapid, and in Figure 16 we can see histological changes that have occurred in the biopsy specimen of a dog taken on the third day after transplantation

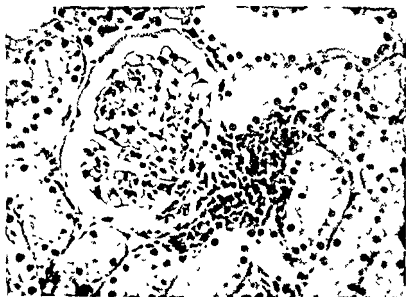


FIGURE 16 A photograph of a homotransplanted kidney biopsy specimen taken on the third day It shows an infiltration consisting of plasma cells Reprinted by permission from Dempster W J A toxic syndrome observed in dogs with transplanted kidneys *Acta med scandinav* 144, *361 (1953)*

better than we expected that I think we now have justification for going ahead with additional studies at the clinical level

Let me acquaint you briefly with the background of the animal experimentation, which goes back almost fifty years Figure 14 is taken from Alexis Carrel s paper of 1902 (4), showing his technique for suturing blood vessels

In Figure 15, you can see the way it was actually carried out by this tridimensional procedure Once he was certain that he could suture arteries and veins in the dog and the cat, he proceeded to a study of various transplantations with emphasis on the kidney

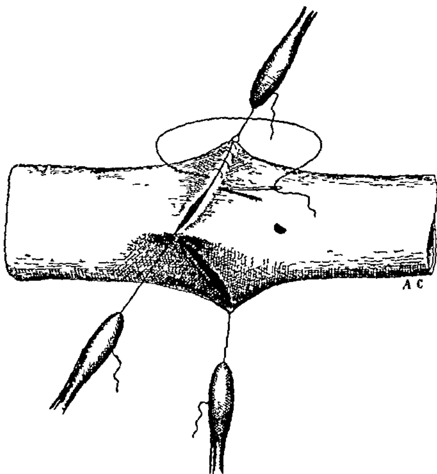


FIGURE 15 A further illustration of Dr Alexis Carrel s method of suturing blood vessels Reprinted by permission from Carrel A La technique operatoire des anastomoses vasculaires et la transplantation des visceres *Lyon med* 98, 859 (1902)

He transplanted kidneys in the cat and in the dog, paying very little attention to the functional results It is difficult, from the protocols, to know what was done beyond the very expert surgical procedure However, by 1907, Carrel (5) had performed a sufficient number of experiments in animals so that he felt there was no problem remaining in human transplantation – except to find donors! He states that he did not know where he could obtain a kidney to give a patient

Unfortunately, he did not realize the tremendous difference that exists between homologous and autologous transplants When C S Williamson (6), in the period from 1922 to 1926, conducted controlled experiments, it was immediately apparent that homologous transplantations in the dog failed very rapidly, whereas the autologous transplants made by precisely the same techniques functioned for months and even years The reaction in the homologous transplant is extremely rapid, and in Figure 16 we can see histological changes that have occurred in the biopsy specimen of a dog taken on the third day after transplantation

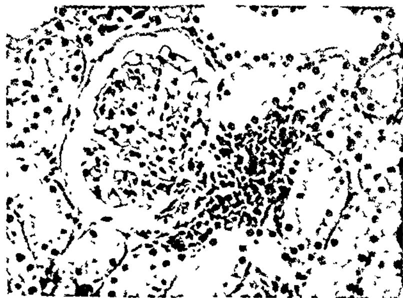


FIGURE 16 A photograph of a homotransplanted kidney biopsy specimen taken on the third day It shows an infiltration consisting of plasma cells Reprinted by permission from Dempster W J A toxic syndrome observed in dogs with transplanted kidneys *Acta med scandinav* 144, 361 (1953)

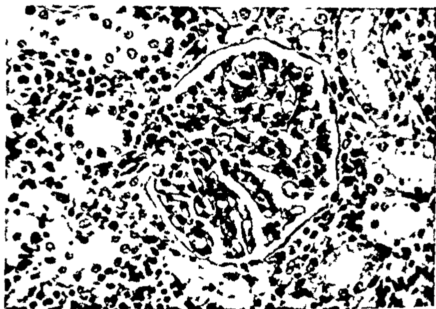


FIGURE 17 A photomicrograph of a homografted kidney which functioned well for 10 days and then stopped secreting The kidney was removed on 11th day In the main the infiltration consists of plasma cells polymorphs enter later and are either signs of infection or are attracted by the devitalized renal parenchyma Reprinted by permission from Dempster W J Replacement surgery symposium tissue homografting *Med Illus* 6, 585 (1952)

Figure 17 was taken when the kidney had failed on the tenth day That was also shown in Williamson s study He worked on the problem for four years investigating many aspects of it and found that ten days was a long period of survival Eighteen was really exceptional, and the average tended to be about five Experiments made since then confirm that period of survival for a homologous kidney transplant in the dog

Very few other species have been studied We have the Carrel work on the cat, which is an extremely difficult animal to handle technically and the rabbit's vessels are even worse There have been one or two transplants in goats, I believe, without any notable differences in survival In the dog transplant, there is urine output almost continuously, and if the suturing is done properly, from the very first day However, on a certain day, usually the fourth or fifth, the kidney swells up the swelling is so marked that it may be detected by palpation The ureter blackens and retracts From then on there is absolutely no function of the kidney This as you will see later, is quite different from what happened in our human transplants

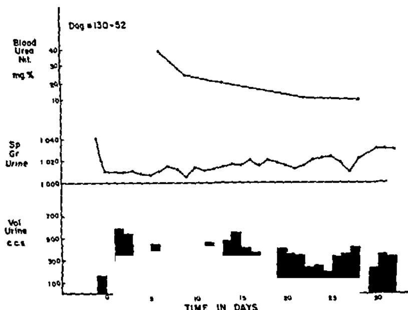


FIGURE 18 Typical course of an autotransplant in dogs

Figure 18 shows the continuation of function which is seen in an autologous transplant in a dog where exactly the same technique is used as in the homotransplant Appreciable function is obtained, enough so that if the other kidney is removed the dog will survive and keep out of uremia Later, usually in about a year, there will be some degree of hydronephrosis, because the ureter is frequently exteriorized in the neck region and the muscles begin to involve the ureter and cause trouble, but the kidney does not fail biologically in the autologous transplant

I should like to show you now rather briefly, some of the results with human transplants* In the human transplants, we have obtained our donor kidneys from almost any source where we could obtain a reasonably healthy kidney We have used operating room

*[illegible] ...ical School performed ...r members Adler and D Moore The studies Company Company

deaths, some cadavers, and occasionally a perfectly normal kidney that had to be removed at operation, particularly in Dr. Donald Matson's (7) neurosurgical procedure in which he removes the kidney in order to connect a tube to the ureter for relief of hydrocephalus He releases the spinal fluid through the urinary bladder When he plans to remove a sufficiently large kidney, we try to have a recipient ready Two of these are included in this series; thus we have had a variety of donors Our recipients have been chiefly patients with terminal pyelonephritis and glomerulonephritis There was one with polycystic disease, and another with periarteritis nodosa

In Figure 19, we can see the type of operation which has been devised and employed by Dr David M Hume The transplant is made into the thigh, the suture lines are indicated in the figure He

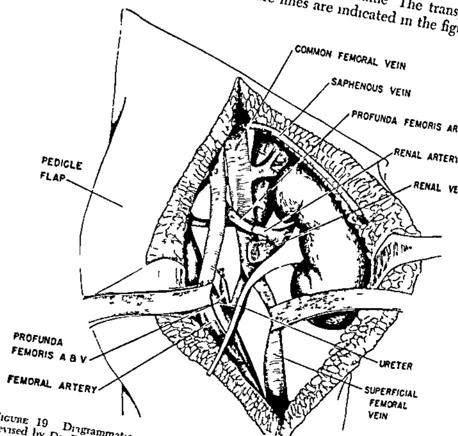


FIGURE 19 Diagrammatic representation of the human transplantation operation devised by Dr David M Hume



FIGURE 20 Orifice of ureter discharging via skin of thigh

uses an end to-end anastomosis for the arteries, and one which is end to side for the veins The ureter is then brought out to the surface of the skin Those details may be seen in Figure 20, which shows the well vascularized ureter Figure 21 presents an x ray of the transplant It is a retrograde pyelogram, in a rather strange place!

Figure 22 shows the completed surgical procedure We attach the collecting unit to a bottle on the floor when the patient is in bed The one patient, who survived long enough to become ambulatory and leave the hospital, strapped a collecting bottle on the thigh He was able to get around three or four hours before he had to empty the collecting unit It worked extremely well

Why did we use the thigh instead of the renal fossa? Some surgeons who have been interested in transplantation, have gone ahead and removed a kidney and replaced it with a homologous graft We have promised nothing We told the families of the patients that there was only one chance in a million that a permanent result would be obtained In most instances, we have been approached by families asking us to do the operation

With the transplanted kidney in the thigh, we know where we stand, but if we put it in the renal fossa, connected to the urinary



Figure 21 Roentogram taken with contrast medium instilled into the ureter and pelvis of the transplanted kidney

bladder there is no way of knowing from which kidney the urine is coming *We decided that our clinical work would have to be kept* on an investigative level i e we had to know exactly what was happening to the kidney from day to day

There are several other advantages in using the site in the thigh We are *adding* a kidney not subtracting anything The patients we selected were at the very end of the road in fact most of them were half way over the life line They had been dialyzed by Dr



FIGURE 22. Kidney transplant discharging urine into the collecting unit

J B Merrill and his group a number of times on the artificial kidney so there was no doubt that we were justified in carrying on this type of research in these instances Also we felt better in not taking out a kidney but instead adding something to the already depleted function

Then there is the problem of infection and hemorrhage With the kidney placed in the thigh we can get at it also it permits biopsy However there are disadvantages in that it is an abnormal place we cannot attach the ureter to the urinary bladder We have wondered too whether or not the temperature effects might be

different We do not mean to imply that this is the only site that we shall ever use but I think we had adequate reasons to start with the transplant in the thigh and we are rather glad that we did so

Now let me run through the results on two of our best patients we have studied ten In one we achieved an unusual degree of function and in another an exceptional duration I wish I could put these two together together it would make a rather nice combination

The first patient was a woman of 50 with polycystic disease and very profound uremia The transplantation was interesting This was one of the early ones in which we thought that the period of renal ischemia would have to be kept at a minimum The donor died early in the morning and the family was not available One must obtain postmortem permission from the family in Massachusetts Therefore by the time it was signed the surgeon summoned and all the procedures carried through two hundred minutes had elapsed from death to the establishment of circulation in the homotransplanted kidney Nothing happened for the first ten days no urine whatsoever was excreted On the 11th day urine appeared

TABLE II

Kidney Transplant

Patient B B Polycystic Disease

Days after Transplantation	Transplant Urine Volume 24 Hours	Blood Urea N
11	25	133
14	1 100	–
15	1 125	–
16	1 560	–
18	2 820	91
21	1 350	65
22	1 660	–
24	1 100	–
25	1 050	–
26	950	41

Table II shows the volumes which reached the unusual amount of 2 820 ml on the 18th day The blood urea nitrogen fell almost to normal and the creatinine at the time when the blood urea nitrogen was 41 mg per 100 ml was down to 2 mg per 100 ml The patient who happened to be the mother of a physician and knew a great deal about her disease would tell us almost every day of a decrease in the toxic symptoms of her uremia Around the 24th day she felt well enough to sit up get out of bed and walk around On the 29th day she had a chill and fever The kidney became infected and from then on progressively lost function and by the 100th day it was so badly infected that it had to be removed We had some function studies in that period that I should like to show you

TABLE III

**Function of Renal Transplant
Compared With Patient's Polycystic Kidneys**

Patient B B 21 Days after Transplantation		
	Inulin Clearance ml per minute	Plasma Flow ml per minute
Polycystic kidneys	2 1	11 0
Transplant	14 4	112 0
Transplant x 2	28 8	224 0
Average normal	126 0	620 0

In Table III we compare the patient s own two polycystic kidneys with the transplant To put the transplant function on a basis that we all understand because we think of two kidneys I have multiplied by two This was 21 days after the transplant opened up I think that Dr Bull and the other experts on tubular necrosis here would probably tell me there was reabsorption of inulin so it is possible that the inulin clearance i e the glomerular filtration rate was considerably higher than indicated in Table III The calculated GFR was roughly one fourth of normal It is possible too that the calculated plasma flow was lower than the true value

Table IV contrasts the urea and creatinine clearances on the transplanted kidney with the patient s two polycystic kidneys The intravenous phenolsulfonphthalein was 22 per cent from the trans

TABLE IV

Kidney on 18th Day After Transplantation

Patient B B Polycystic Disease

Test	Transplanted Kidney	Patient s Polycystic Kidneys
Urea clearance	64 ml per minute	25 ml per minute
Creatinine clearance	185	58 "
PSP (Intravenous)	22 per cent in 2 hours	1 per cent in 2 hours

plant as compared with one per cent from the two polycystic kid neys In this patient we were fortunate in achieving a very high degree of function higher than in any other patient in our series By the time the kidney was removed it was so badly infected that the pathology is of rather minimal interest as compared to that of the next case

The second patient was a young physician who came to us from South America As he was graduating from medical school he had discovered that he had severe hypertension and also his renal func tion was reported to be 11 per cent by urea clearance He had a fundal hemorrhage and was told by his physician that he should come to Peter Bent Brigham Hospital with the thought of having a transplant performed Before he arrived we had had some dis cussion about possible types of immune reactions in the homotrans plants In a number of the dog experiments that had been carried on by Dr David Hume Dr Joseph Murray, and others in our group it had been noticed that within a few days there was a very marked reaction around the transplanted kidney We wondered whether cells carrying antibodies might be coming into the kidney from the host by that mechanism Dr Hume then suggested that it should be possible to transplant a kidney and wrap it in an inert plastic bag so that it would not have any contact with the host He dis cussed it with the physician patient who agreed to it In this patient we were also alerted to the infections that had set in with pre vious transplants so we put him under strict regulations which were the same as those that would be used in the case of a surgical patient with an extensive burn That may have made some difference

The period of renal ischemia in this patient was almost 200 minutes The operation performed on February 11 1953 went

extremely well The donor died during surgery for the relief of a mitral lesion The kidney survived for a period of five-and-a-half months, the blood urea nitrogen dropped to 33 mg per cent shortly before the patient died This transplant, the latest in our series, began to produce urine on the 19th day, and it increased its urinary output to about 1,200 to 1,500 ml, which was maintained for a number of months Unfortunately, the severe hypertension which he had had before the operation was not significantly affected by the homotransplant, and we believe that the patient died from a reaction to his blood pressure Just prior to death he had a diastolic pressure of from 140 to 150 mm Hg We tried everything within our power to reduce his blood pressure, but were unsuccessful Dr Robert W Wilkins, of Boston University Medical School, saw the patient and prescribed various experimental agents but nothing seemed to make any difference

TABLE V*

Patient G. W.: Chronic Glomerulonephritis

	ml. per minute per 1 73 sq meters of body surface	
	Inulin Clearance	PAH Clearance
Bladder	5 6	32
	4 8	24
Transplanted Kidney	6.8	32
	7 4	32

Inulin and p aminohippurate (PAH) clearances were performed approximately two months after the transplantation operation, and again at four months In Table V the averages are given for each of these time intervals As you can see, the function is not phenomenal, but, as we all know, not a great deal of renal function is needed to sustain life Apparently, these small increments were of great help to this patient

In Tal [illegible]

nitrogen [illegible]

after op[illegible]

*The data in Tables III IV and V were kindly furnished us by Dr John Finkenstaedt

TABLE VI

Patient G. W.: Chronic Glomerulonephritis

	Blood Urea Nitrogen Mg per cent	Hematocrit	Total Urine Volume
Before Operation	80 to 100	30	1,800 ml
5 Months after Transplant	33	41	3 000 ml

he died a level of 33 was obtained The hematocrit improved at that time and the total volume of the bladder and the transplant amounted to about 3,000 ml per day It was during this period that he felt so well, enjoyed food as he had not done for a very long time and had considerable vigor On a hot summer day, he ran for a bus and did not collapse He really surprised us

The postmortem examination revealed a relatively well nourished ureter, a healthy venous anastomosis The arterial anastomosis showed no cellular reaction In several patients the anastomoses of both the arteries and veins have looked remarkably healthy In the renal capsule there was a fibrotic reaction at the periphery, and then healthy glomeruli Dr Dammin said he thought there were quite a few essentially normal nephrons that had survived the five-and-a-half month period He found a thickening of the glomerular basement membrane in this transplanted kidney, more than there had been in the donor's other kidney, in which there was passive congestion

We were surprised, in comparing these results with dog transplants to note how much intact architecture remained in some of these kidneys Dr Dammin said that there were a number of quite intact tubules, interstitial edema, and focal interstitial cellular infiltrate in the cortex and medulla of the transplanted kidney The plasma cells of the infiltrate had pyronin positive cytoplasm The architecture was essentially preserved, and the tubular epithelium particularly in the medulla was moderately well preserved

In an examination of the patient's own kidneys, we observed chronic nephritis with glomeruli which had been destroyed In microscopic sections of the ureter, we were particularly interested to see how well the ureter was nourished and preserved In homotransplantation studies, this is most fascinating, because there the host and donor tissues can be seen living side by side, apparently

very compatibly There is a minimal reaction where the host epithelial tissue had grown over the ureter

Dr Dammin pointed out particularly the good appearance of the smooth muscle in an area of the transplant at the lower portion of the ureter Smooth muscle does not regenerate so it is reasonably certain that this was from the donor s ureter as originally put in and that it had lasted five and a half months I think that in itself is a very hopeful omen for the future of kidney transplantation Under high power a certain number of macrophages were observed but generally there was no explosive reaction of any sort

In this patient although there were breaks in the elastica there was no marked cellular reaction to the suture line at the venous anastomosis A high magnification of the venous anastomosis showed the minimal amount of cellular reaction of host and donor tissue at that particular point

There was a very good solid union at the arterial anastomosis We could really tug at these during the postmortem examination and they would not come apart The transplanted artery beyond the site of anastomosis showed differences from the host artery i e a rather thick intima and a reversal of the usual ratio of intima to media Some very interesting changes occurred in the blood vessels of the transplant during the five-and a half month period The degree of atherosclerosis was quite extreme macrophages were observed with lipid degenerative material in the vessel and there was a marked narrowing of the lumen

The patient s own nephritic kidney had a considerable atherosclerosis but Dr Dammin felt that it was much less than that which had occurred in the transplant In five and a half months the trans plant for some reason had developed a much greater degree of arteriosclerosis than the patient s own kidneys which had been exposed to nephritis for sixteen years and hypertension for at least several years

Table VII brings us back to much less spectacular material The first patient F A received as a transplant a normal kidney which had to be removed at operation because there was a tumor of the adjacent ureter Dr Merrill s group got the patient ready on the artificial kidney Then the donor kidney became available in Spring field Massachusetts where the patient came from His physicians there Drs J V Schola and L H Doolittle actually transplanted the kidney and sent him back to the Peter Bent Brigham Hospital in Boston where we took care of the patient after that The period of ischemia was estimated to be 70 minutes This transplant was the

TABLE VII

Transplantation Kidneys — 9 Cases

Patient	Blood Type of Recipient	Blood Type of Donor	ACTH or Cortisone	Duration Ischemia	Function of Trans plant
F A (37 Years)	A+	A+	+	70′	±
M P (30 Years)	O+	A+	+	150′	0
F Z (43 Years)	B+	B+	+	135′	++
B B (52 Years)	O+	O+	+	200	++
D P (18 Years)	O+	O+	+	55′	++
B L (24 Years)	O+	O+	0	14′	+→0
D G (28 Years)	B+	O+	0	200′	0
O F (57 Years)	O+	O+	+	275′	0
G W (28 Years)	A+	A+	0	150′	+

only one in the series in which the kidney was placed internally, in the renal fossa A T-tube was placed in the ureter, and brought out in the patient's flank It was rather difficult to know when the urine was coming from the transplant, and when it was refluxing from the bladder We cannot be certain, but we think the transplant began to excrete about the 12th or 14th day, and continued to put out some urine thereafter The transplant function was not sufficient to alter the blood urea The patient died on the 37th day after the transplant, not so much from uremia as from pleural infection His kidney was not markedly infected, as in many of the subsequent patients



FIGURE 23 Patient F A Gross appearance at postmortem examination of the transplanted kidney The anastomosis of the arteries can be seen

Figure 23 shows the gross pathology at the postmortem examination, and here we can see the good clean junction on the arterial side The kidney had a normal gross appearance It also felt surprisingly normal very different from what is seen when a postmortem is performed at the end of a homotransplant in a dog is examined at postmortem Dr Clinton van Z Hawn who was the pathologist at the Peter Bent Brigham Hospital at that time, stated that approx



Figure 24 Patient F A Microscopic section taken through the cortex at post mortem examination 37 days after transplantation of the kidney

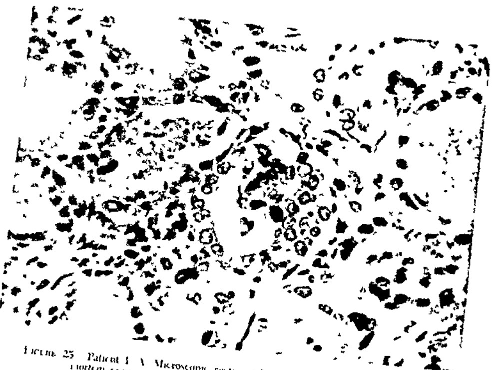


FIGURE 25 Patient 1 A Microscopic section taken through the medulla at post mortem examination 37 days after transplantation of the

mately 50 per cent of the glomeruli appeared normal on a morphological basis (Figure 24) Figure 25 shows more of the tubules from this same patient (F A) at the 37th day after the transplant

The next patient (M P), listed in Table VII, showed no function The transplanted kidney was infarcted Whether that was due to the incompatible blood types, we do not know, we had a few of these in the series We sometimes did this out of sheer desperation because the patient had been promised a transplant and we did not have a donor with compatible blood, also, we did not know whether or not blood typing was essential, and we still do not know However it is interesting that in the cases in which the blood types were not compatible, the transplanted kidneys never functioned and were infarcted at postmortem

The next patient, F Z , in Table VII, was a particularly interesting one Early in the series, before the surgeons realized how much space an adult kidney took up in the thigh, a relaxing incision or proper flaps were not made in advance, as is now the practice In this patient the skin closure was made, but the skin sloughed away, infection set in, and it was really a horrible sight to see that kidney It did open up on the 11th or 12th day, put out urine, and continued to do so for at least 70 days On the 70th day, we performed a



FIGURE 26 Patient F Z Biopsy of the transplanted kidney taken on the 70th day after operation

biopsy I recall this operation very vividly I had thought the kidney would be almost bloodless, but the surgeon must have hit a good-sized vessel, because there was a small geyser of blood that leaped up as he took out a piece of kidney tissue The ureter had been caught up in the infection and had sloughed back to the pelvis of the kidney

This case gave us some idea of the tremendous vitality of these human homotransplants Figure 26 shows the biopsy that was performed on the 70th day The infection was tremendous at that time, and yet we see recognizable structures in this kidney There was urine that seeped out each day and if we put in PSP, we would get a little trace, indicating there were some intact tubules On the 18th day, Dr Hume performed the test with aminophylline, and showed that there was some response in the homotransplant (Figure 27)

Table VIII shows the modest degree of function in patients D P and F Z Neither of these had sufficient function to affect the blood urea but they put out reasonable amounts of urine

Patient D P in Table VII was particularly interesting because she was the first for whom a normal kidney was obtained from a young donor Dr Donald Matson had to remove a kidney from a

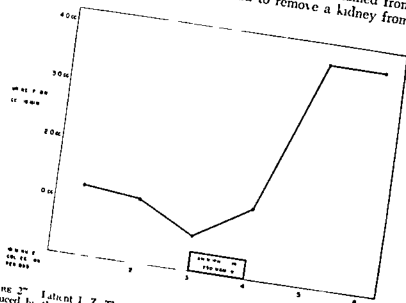


FIGURE 27 Patient F Z The increase in urine flow from the transplanted kidney produced by the intravenous injection of 250 mg of aminophylline

mately 50 per cent of the glomeruli appeared normal on a morphological basis (Figure 24) Figure 25 shows more of the tubules from this same patient (F A) at the 37th day after the transplant

The next patient (M P), listed in Table VII, showed no function The transplanted kidney was infarcted Whether that was due to the incompatible blood types, we do not know, we had a few of these in the series We sometimes did this out of sheer desperation because the patient had been promised a transplant and we did not have a donor with compatible blood, also, we did not know whether or not blood typing was essential, and we still do not know However, it is interesting that in the cases in which the blood types were not compatible, the transplanted kidneys never functioned and were infarcted at postmortem

The next patient, F Z, in Table VII, was a particularly interesting one Early in the series, before the surgeons realized how much space an adult kidney took up in the thigh, a relaxing incision or proper flaps were not made in advance, as is now the practice In *this patient the skin closure was made, but the skin sloughed away*, infection set in, and it was really a horrible sight to see that kidney It did open up on the 11th or 12th day, put out urine, and continued to do so for at least 70 days On the 70th day, we performed a



Figure 26 Patient F Z Biopsy of the transplanted kidney taken on the 70th day after operation

kidney This was a 35-year old patient We were able to time things perfectly Dr Macgregor performed the transplant over tubes in other words he sutured the vessels with plastic tubes in place permitting flow of blood The period of ischemia was 14 minutes! After he had all his ligatures placed he withdrew these tubes and made his closures

We had the greatest hopes that this procedure would show some thing unusual yet this kidney never functioned We are not sure that the conditions around the organ were the same as in the other transplants It was a very large kidney Dr Macgregor felt that instead of taking a chance with the sloughing of the surface tissues he would undermine some of the muscle in the thigh which he did to form a very nice bed for the transplant But unfortunately there was an enormous amount of seepage of lymph and blood We thought that possibly there was enough tension to compress the kidney so it could not function because of pressure but we are not sure about that

Patient O F in Table VII apparently had total destruction of the kidneys due to generalized periarteritis nodosa She had been dialyzed so many times on the artificial kidney by Dr Merrill and his group that they felt they could do nothing more The family wanted a transplant performed

No urine was ever excreted by the transplant The patient died 38 days after the operation had been performed At postmortem we found some very interesting things

Figure 28 shows an extensive glomerulonephritis set up in the transplant Perhaps Figure 29 shows it a little better Figure 30 shows the patient s own kidney

Dr Clinton van Z Hawn who has had a great deal of experience with both human and experimental nephritis felt very certain that a true glomerulonephritis had been set up in the transplanted kid ney similar to the process in the patient s own kidneys I should like to ask this group whether they can conceive that the exceptionally long period of ischemia could have caused that strange pathologic reaction in the transplant? There was an unusual delay in reaching the family of the donor for the postmortem permission This was the longest period of ischemia in our series If ischemia was not the cause I think we have suggestive evidence that there was a circulat ing factor in this patient s blood stream which affected the trans plant and produced a glomerulonephritis

Dock Was no attempt made to lower the temperature of the donor kidneys during these hours? Did you just let the body tem

TABLE VIII

Patient D P 6 20 51 – 20th Postoperative Day BUN 128				
	24° Vol	Cl mEq/L	Creatinine mg per cent	Urea N mg per cent
Bladder Urine	180	13	67	519
Transplant Urine	780	33	45	615

Patient F Z. 5 13 51 – 19th Postoperative Day BUN 148					
	24° Vol	Na mEq/L	K mEq/L	Creatinine mg per cent	Urea N mg per cent
Bladder Urine	580	16 2	35	44	832
Transplant Urine	600*	3 5	47	52	1023

*Not complete

two year old child during a neurosurgical procedure to relieve hydrocephalus We were able to time things so that we had our recipient ready in the adjacent operating room As soon as he removed the kidney it was handed to Dr David Hume for transplantation The period of ischemia was relatively brief In the first 24 hours the transplant put out 1 600 ml of very watery urine The next day there was 150 ml Then a period of anuria intervened such as we have observed in other patients However on the twelfth day urine again began to be excreted There was a good deal of infection the patient was in profound uremia to start with and also had infection of the other thigh After a period of function of twenty or thirty days the transplanted kidney became so badly infected that there was no excretion of urine A very unusual situation was seen in patient B L (Table VII) We were very eager to see what would happen if we could reduce the period of ischemia to practically zero Dr Charles Macgregor who was taking over as the surgeon while Dr Hume was away had a suitable donor for our purpose This happened to be one of the rare instances when Dr Donald Matson operated on an adult patient for relief of hydrocephalus employing his procedure which requires removal of one



FIGURE 29 Patient O F Section taken from the transplanted kidney



FIGURE 23 Patient O F Section taken from the transplanted kidney

perature fall in these corpses without putting in cold saline or doing anything?

Miller We thought of it, but it just was not feasible

Dock You started with a normal or elevated temperature, and it dropped gradually over the period that you waited?

Miller Yes We did not perfuse the donor kidneys as a rule Dr Hume was worried that we might traumatize the intima of the blood vessels In some we infused heparin and/or antibiotic, but we generally did very little Actually, there was no apparent clotting

Bull How long was cortisone or ACTH given to most of these patients

Miller In the first several patients, we gave both usually for several weeks However, we varied this a good deal Then, recently, we gave them up altogether, we do not think there was any effect that could be determined They were not given at all in the patient whose kidney survived five and a half months

Lawson Did you give it in that case of periarteritis nodosa where the patient had active renal disease at the time of the transplant?

Miller Yes We had to do a certain number of rather drastic things to get the project moving Now that we feel we have had enough success to warrant its continuation at both the clinical and the laboratory levels, we are planning to go back, in the next group, to the situation we should have preferred from the start, which is not to do anything except give the antibiotics and those things which are essential to save the patient's life We are not going to use any modifications and therefore we shall probably learn the true natural course of a human kidney transplant

Oliver Of course, in all but the cases of the polycystic kidneys, you are in what appears to be an impossible situation You are putting good kidneys into people whose peculiarity it is to destroy them

Miller You are referring to the "presumptive" antibodies circulating in human glomerulonephritis, not to antibodies evoked by the transplant We have worried about that I am sure that would be the case if we made transplants during the early stages of glomerulonephritis However, we select only people at the terminal stage One would think from the results that we obtained in the young physician G W who had definite glomerulonephritis that by the time this disease reached the terminal stage – this was sixteen years after the onset which he could date quite accurately – the "glomerulonephritis antibodies" were not able to destroy the transplanted kidney We would think that where a transplanted kidney had

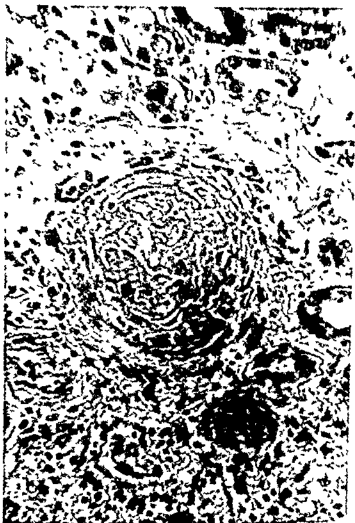


FIGURE 30 Patient O F Section taken from her own kidney at biopsy before the transplantation procedure

the young physician who went on so long and did not respond with a typical antibody reaction

Dock It almost looks as though the longer the kidney remains in a dead body, the better chance there is of its surviving in the recipient, does it not? I suppose the transplant was done rapidly in the case of the French boy?

Merrill Yes

Miller Except in ideal circumstances, we have been forced to ait longer than we wished to perform transplant operations Yet ome of the best transplants seem to result from ischemic kidneys, it may be that the longer period of ischemia has something to with the good effects we obtained

Dock The experiments seem to indicate that your best survivals in kidneys that have become very cold in the body before they are taken out

Miller Another factor which is interesting, and I would like to get your reaction to it, is that three of the best results were obtained in kidneys that were taken from donors who had suffered from chronic heart disease They had had a good deal of cyanosis and passive congestion

Dock We can reproduce these conditions in a dog by killing it, and taking out the kidney at 100 and 150 minutes to see whether it lasts longer than the ones taken out immediately Have quick transplants been done in all the dog experiments?

Miller We have just started the experiment where we vary the period of ischemia We let the donor dog die and permit the body to cool down to simulate the clinical situation I wish I had some results to tell you about but it will be some months before data are available We are also going to prepare some dogs with chronic heart failure and see if the cyanotic congested donor kidney might be an important factor

The question has also come up about the effect of uremia Some people in our group have felt that the chronic uremic patient manufactures antibodies at a slower rate than the normal individual It is possible that just because a patient has the right degree of uremia he may not be able to reject the kidney transplant Then later if he achieves a good function like patients B B and G W in Table VII we reach the stage where the antibodies can be regenerated and the kidney is destroyed That is a fearful prospect I hope that theory is not true

Pressman I think it is I cannot comment about antibody formation in the case of uremia, but I think it is rather remarkable that

survived for five and a half months it had probably gone beyond the period of antigen antibody sensitization In patients with pyelonephritis this danger should not be present unless this disease sets up an antibody reaction in its chronic stages

Dock The sections bear that out

Oliver But in the case of glomerulonephritis in the transplant it seemed almost a demonstration that the nephritis producing substances were still there

Dock At least in cases of periarteritis

Miller Oh yes Or if we took a patient with acute glomerulonephritis I should imagine that we would destroy the transplant

Berliner That is not necessarily true if nephrotoxic serum nephritis is in any way analogous Of course it may not be but if one does not clamp one kidney but instead injects nephrotoxic serum and then take off the clamp the kidney that was clamped never develops nephritis

Oliver But the animal is not making the nephritis producing substances

Berliner We do not know that the patient with nephritis is making antibodies either Although the renal disease may be progressive it is possible that all of the necessary damage is produced at one time

Dock At any rate we have had no chance to do this on a hypertensive patient with one pyelonephritic kidney If the blood pressure fell perhaps atherosclerosis would not develop so fast and periarteritis or glomerulonephritis would not appear

Merrill There was a case in France of a young boy with no previous renal disease but with only one kidney which was traumatized it was removed by mistake before it was discovered that he had none on the other side A kidney from his mother was transplanted into the renal fossa of the boy which functioned for three weeks very well and then suddenly stopped In that situation there was no question of pre existing nephritis or indeed of anything that affected the other kidney because it simply was not there

Dock I did not mean that We do not like to have transplantations complicated by atherosclerosis or Bright s disease which makes the histology very confusing In the boy the kidney had been injured

Merrill I think perhaps the discouraging thing about the particular case of the French boy was the fact that the pathology resembled that of the dog

Miller That is interesting because it was different from that of

gation concerning antibodies has intrigued me for some time but I have not known how to go about handling the problem in man One might try to elute antibodies out of the kidneys which are ing through a change radioiodinate the extract label it reinject into another individual and see whether it contains material capable of localizing in the kidney of the recipient The background for that experiment is the following (9) If we prepare antibodies against a rat kidney in rabbits label them with radioactive iodine and inject them into a rat there is localization of the antibodies in the kidney These kidneys can be removed radioactive antibodies eluted from the kidney and reinjected into another rat and it will localize again in the kidney Now if the situation in the human is such that there are antibodies which have localized in the kidney we might well be able to elute the antibodies from the kidney tissue label them and inject them into another individual who is to have kidney removed surgically and look for uptake in that kidney One reason why I think this is an important experiment is that one ay not be able to find antibodies in the circulation since they y have been removed by the kidney as rapidly as they were med (10) The place to look for such antibodies would then be in the kidney This is a somewhat complicated experiment but I do not see why it cannot be done

Dock There may be blocking antibodies in the blood also which would be very difficult to eliminate

Pressman So-called blocking or univalent antibodies would prob ably be localized also

Dock They could go on into the kidney

Pressman Moreover if there is an excess of antibodies still in the circulation they could be demonstrated by labelling and testing serum for localizing activity

Miller Dr Pressman do you know the work of Drs Kaliss and Snell (11) on the factor in blood that is supposed to alter individual specificity? We wondered whether the large number of blood trans fusions received by our patients at the time of the operation and in the days thereafter might explain the significant difference between the dog and human transplants

Pressman Are you talking about the work on enhancement of tumor growth by previous immunization?

Miller Yes

Pressman I do not think that any factor has been isolated as yet In those experiments mice were inoculated with lyophilized tumor tissue and then subsequently an implant of a live tumor pellet

these kidneys which ceased to function seemed healthy whereas one certainly would suppose that with antibody formation against the kidney there would be more evidence of subsequent reactions However what we have here does not seem to be precisely the same reaction that we observe in the case of the disease in rats

Dock The change in the dog kidney with the higher infiltration in the glomerulus was quite different from that produced by Masugi nephritis

Pressman Human kidneys do not have these lesions either I was wondering whether there might be an antibody activity taking part in this reaction but a very subtle one resulting not in definite lesions in the kidney but in just a cessation of function In the case of skin transplants from one animal to another some skin transplants will last much longer than others eventually sloughing off I do not know the nature of the lesions that first form in the sloughing of the skin transplant but they may be rather subtle We may have the same type of reaction taking place here an actual antibody formation but not necessarily of the type that produces glomerulonephritis (if glomerulonephritis is produced by antibody action) It may interfere with certain enzyme activities and subsequent stoppage of activity of the kidney

Bradley Have you any evidence for the production of antibodies to kidney tissue?

Miller The problem is to obtain a suitable antigen and a sensitive method In our group we have an immunologist Dr Frank Adler who is trying to find individual specific antigens That is quite a problem He appears to be making some progress at the moment Crude indices of antigen antibody reaction such as the serum complement level have not worked out even in the dog homotransplants We were hopeful that the same type of reaction that we find in an acute glomerulonephritis with the complement level dropping almost to zero might occur at the time when the dog homotransplant fails Our group carried out a study on that and we could not observe any drop in the complement at that time (8) Simonsen (23) in Copenhagen also noted the same results in 1953 We have carried through some complement determinations in the patients but they have not shown us anything very definite I should be extremely grateful if somebody could make a practical suggestion because it is a pity not to have the techniques to tell us whether or not at the point of failure of the transplants there is an antigen antibody reaction that sets in

Pressman The possibility of carrying out a certain type of investi

the transplanted kidney, during the anuric phase, by measurements of skin temperature over the mass?

Dock You made no effort to collect renal vein blood? You do not put a marker around the renal vein so you can collect from that and see what it is?

Miller We wished to, but we have not dared go into the transplant vessels

Dock In the dog, we do not have to do this because they function so well

Miller The dog is so different that comparisons would probably be meaningless

Dock Perhaps the dog kidneys will do the same thing, if they have seventy or eighty minutes of ischemia before they are transplanted

Miller One or two experiments are insufficient for drawing any conclusions

Oliver Some of the tubular epithelium in the kidneys certa looked like regenerated epithelium Perhaps in the earlier per of lack of function, there may have been tubular damage, and th there occurred repair with functional recovery and regeneratio That might account for some of those queer-looking tubules, the do not look at all like the original tubules of the kidney

Bull Does the kidney swell in that period of oliguria?

Miller No, not that we can detect clinically

Dock Any swelling that occurs is there a few minutes after the transplant and during the next few days, it does not swell?

Miller No

Pressman Has anyone tried skin transplants in dogs? If there is a much more rapid sloughing off of skin in dogs than with skin transplants in humans, that may be a reflection of the same type of process which is taking place more rapidly with dog kidneys

Miller There has been some very interesting work by both W J Dempster (1) and M Simonsen (23) on that There is a factor, apparently common to skin and kidneys One can homograft a piece of skin on a dog Then if one transplants the kidney from the same donor that provided the skin he will obtain an explosive rejection of the kidney An accelerated reaction has been caused by the skin, and the kidney may be rejected within less than a day In our human studies, we have been afraid to put skin on from the same donor at the time of the kidney transplant for fear we would sensitize the kidney We should like to try saving skin from the donor, and then, in some instances, when the situation is hopeless put some of the

would grow and kill the animal, whereas previously the tumor would grow initially but then regress

Miller If I remember correctly, Dr Snell stated that the principle could be found in blood, in fact, he wondered whether the reported successful homotransplantation of skin might have been influenced by the large number of blood transfusions that were given

Pressman Snell (12) quotes evidence to that effect

Miller How do you react to the plastic bag as a significant factor?

Pressman I do not think the plastic bag is a factor at all, because there is certainly contact of the body with the new kidney through the blood stream and plenty of opportunity for phagocytic or other migratory cells to pass through the kidney

Lauson Was there as much scarring around the kidney when the bag was in place as when it was not present?

Miller There is not a great deal of scarring around the human transplants that we have seen We have noticed recently that the location of the homologous transplant in the dog seems to determine this capsular reaction When the transplant is made in the neck, we do not seem to obtain that reaction It apparently depends on the location in the peritoneal cavity We are therefore inclined to pay less attention to it now

Taggart What do you think happens on the tenth day that permits the kidney, once shut down, to open up again? In the case of acute tubular necrosis, we should say that reparative processes were occurring, but can we say the same here?

Miller The human transplant does seem to go through a shut down like an acute tubular necrosis, and then open up Only in the case of Mrs B B, the patient who had approximately 30 per cent inulin clearance, did we obtain anything approximating the high rate of recovery that we see following this condition We think that something like a tubular necrosis has occurred, with an attempt at recovery This is very different from the course in the dog

Dock The dog kidney functions from the beginning?

Miller Yes, and then stops explosively and does not open up again

Burnett Have you biopsied any of these kidneys during this shut down period?

Miller We have not dared risk it as yet

Taggart Can one learn anything about the blood flow through

the transplanted kidney, during the anuric phase, by measurements of skin temperature over the mass?

Dock You made no effort to collect renal vein blood? You do not put a marker around the renal vein so you can collect from that and see what it is?

Miller We wished to, but we have not dared go into the trans plant vessels

Dock In the dog, we do not have to do this because they function so well

Miller The dog is so different that comparisons would probably be meaningless

Dock Perhaps the dog kidneys will do the same thing, if they have seventy or eighty minutes of ischemia before they are trans planted

Miller One or two experiments are insufficient for drawing any conclusions

Oliver Some of the tubular epithelium in the kidneys certainly looked like regenerated epithelium Perhaps in the earlier period of lack of function there may have been tubular damage and then there occurred repair with functional recovery and regeneration That might account for some of those queer-looking tubules they

Dock Any swelling that occurs is there a few minutes after the transplant, and during the next few days it does not swell?

Miller No

Pressman Has anyone tried skin transplants in dogs? If there is a much more rapid sloughing off of skin in dogs than with skin transplants in humans that may be a reflection of the same type of process which is taking place more rapidly with dog kidneys

Miller There has been some very interesting work by both W J Dempster (1) and M Simonsen (23) on that There is a factor, apparently common to skin and kidneys One can homograft a piece of skin on a dog Then if one transplants the kidney from the same donor that provided the skin he will obtain an explosive rejection of the kidney An accelerated reaction has been caused by the skin, and the kidney may be rejected within less than a day In our human studies, we have been afraid to put skin on from the same donor at the time of the kidney transplant for fear we would sensitize the kidney We should like to try saving skin from the donor, and then in some instances, when the situation is hopeless put some of the

would grow and kill the animal, whereas previously the tumor would grow initially but then regress

Miller If I remember correctly, Dr Snell stated that the principle could be found in blood, in fact, he wondered whether the reported successful homotransplantation of skin might have been influenced by the large number of blood transfusions that were given

Pressman Snell (12) quotes evidence to that effect

Miller How do you react to the plastic bag as a significant factor?

Pressman I do not think the plastic bag is a factor at all, because there is certainly contact of the body with the new kidney through the blood stream and plenty of opportunity for phagocytic or other migratory cells to pass through the kidney

Lauson Was there as much scarring around the kidney when the bag was in place as when it was not present?

Miller There is not a great deal of scarring around the human transplants that we have seen We have noticed recently that the location of the homologous transplant in the dog seems to determine this capsular reaction When the transplant is made in the neck we do not seem to obtain that reaction It apparently depends on the location in the peritoneal cavity We are therefore inclined to pay less attention to it now

Taggart What do you think happens on the tenth day that permits the kidney, once shut down, to open up again? In the case of acute tubular necrosis, we should say that reparative processes were occurring, but can we say the same here?

Miller The human transplant does seem to go through a shut down like an acute tubular necrosis, and then open up Only in the case [illegible] 90 per cent muli [illegible] gh rate [illegible] at something like a tubular necrosis has occurred with an attempt at recovery *This is very different from the course in the dog*

Dock The dog kidney functions from the beginning?

Miller Yes, and then stops explosively and does not open up again

Burnett Have you biopsied any of these kidneys during this shut down period?

Miller We have not dared risk it as yet

Taggart Can one learn anything about the blood flow through

the transplanted kidney, during the anuric phase, by measurements of skin temperature over the mass?

Dock You made no effort to collect renal vein blood? You do not put a marker around the renal vein so you can collect from that and see what it is?

Miller We wished to, but we have not dared go into the transplant vessels

Dock In the dog, we do not have to do this because they function so well

Miller The dog is so different that comparisons would probably be meaningless

Dock Perhaps the dog kidneys will do the same thing if they have seventy or eighty minutes of ischemia before they are transplanted

Miller One or two experiments are insufficient for drawing any conclusions

Oliver Some of the tubular epithelium in the kidneys certainly looked like regenerated epithelium Perhaps in the earlier period of lack of function, there may have been tubular damage and then there occurred repair with functional recovery and regeneration [illegible] bules, they

Dock Any swelling that occurs is there a few minutes after the transplant, and during the next few days, it does not swell?

Miller No

Pressman Has anyone tried skin transplants in dogs? If there is a much more rapid sloughing off of skin in dogs than with skin transplants in humans, that may be a reflection of the same type of process which is taking place more rapidly with dog kidneys

Miller There has been some very interesting work by both W J Dempster (1) and M Simonsen (23) on that There is a factor, apparently common to skin and kidneys One can homograft a piece of skin on a dog Then if one transplants the kidney from the same donor that provided the skin he will obtain an explosive rejection of the kidney An accelerated reaction has been caused by the skin, and the kidney may be rejected within less than a day In our human studies, we have been afraid to put skin on from the same donor at the time of the kidney transplant for fear we would sensitize the kidney We should like to try saving skin from the donor, and then in some instances, when the situation is hopeless, put some of the

preserved skin on the recipient and see whether or not there is an *accelerated rejection of the skin*

Pressman I asked the question from a different point of view Did Simonsen inject the skin, or did he do a skin transplant?

Miller He did a skin transplant

Pressman How long did it last? That would be rejected eventually, too, would it not?

Miller Yes

Pressman How soon was it rejected?

Miller In a matter of days, I believe

Pressman Now, what is the period of time for rejection of human skin transplanted to another human? Does that last for a while?

Miller It lasts for several weeks, I think the longest stayed about 120 days

Pressman There we have the same factor between dog skin to dog, and human skin to human, that we have between dog kidney to dog, and human kidney to human

Miller I do not know whether the time relation would be that exact, there have not been enough skin transplants carried out in dogs so that we can actually say

Pressman If this hypothesis holds up, the skin should be rejected by the dog rather quickly

Bull In Patient G W you mentioned earlier that there was a blood urea of 80 prior to operation, then it rose to 200 immediately after operation, and subsequently fell to 33 Was that a regular phenomenon?

Miller Only during the period of operation The patient was usually critically ill for a few days His own kidneys were not functioning well, and the transplant was not doing anything so the uremia was greatly intensified

Bull Was it just due to operative shock, or was there some other cause?

Miller I should think it would happen merely as a result of the operation

Merrill I think it is quite characteristic in uremic patients who undergo major surgery, whether or not they have a transplant

Berliner Haven t some of these patients been put on an artificial kidney first?

Merrill Some have, and some have not But certainly not within so short a time that we would expect it to be on a rebound simply from the procedure

Bradley What happens to the excretion of electrolytes?

Miller The patient whose kidney functioned for five-and-a half months, altered the abnormal electrolyte pattern and brought it back to normal His potassium became normal

Burnett Could they concentrate this urine, or was it always dilute?

Miller It was always dilute

Bull Does it respond to pitressin and water loading?

Miller Only sluggishly

Bradley Does it respond to mercurial diuretics?

Miller We have not used mercurial diuretics I mentioned one case in which aminophylline was tested

Pitts Dr Oliver, can you recall the length of time that Phillips 13) found a dog kidney could survive ischemia?

Oliver It was three hours

Pitts When it was longer than three hours, was there necrosis?

Oliver Usually

Pitts Without any restoration of function?

Oliver There might be some temporary functional recovery but in the end the dog died of renal failure

Forster Was survival dependent on the temperature at which the tissues were maintained, or was that done only at body temperature?

Oliver They did the experiments at body temperature, I presume

Miller There was some relationship with the season of the year When the experiments were carried out in the heat of summer, the period of survival was shortened somewhat

I should think from what we have seen that the human kidney is a good deal hardier than is suggested in Dr Homer Smith's monograph (14)

Swan He says the general feeling among urologists is that the renal artery should not be clamped for a period longer than 30 minutes but he mentions instances in which there has been no serious impairment of renal function following clamping of the renal artery for a longer period

Pressman Your experiments with cortisone were designed to keep antibody formation down, I suppose?

Miller We had that hope, but like the studies made on dog homotransplants (15), it actually made no difference whatsoever We are hoping to give large amounts of cortisone directly at the site of the transplant, or in the transplanted kidney, and find out whether that will change the results I do not recall that it has been tried as yet

Forster Is there no relationship between the extent of inbreeding in strains of dogs, and the success of maintaining homotransplants?

Miller Not a great deal in dogs, at least Dempster's experiments on greyhounds showed that their survival was exactly the same as the mongrels used by Simonsen However, if we could work with identical twins, then we should achieve survival of homotransplanted skin, and presumably of the kidney and other organs

Forster There is no animal larger than the mouse in which this has been done?

Pressman Dr Medawar (16) did his skin transplantations on rabbits, but they have not been inbred as far as mice Neither have dogs I have heard that even with mice which have been quite intensively inbred, the reciprocal takes are not 100 per cent But this may be a technical problem With inbreeding, as the animals become closer and closer in their composition, there has been a greater time elapsing before the graft breaks down

Dock Is this a peculiarly mammalian problem? I remember that Dr Danforth (17), at Stanford University, used to experiment with birds of strange plumage He transplanted barred feather skin to plain birds, and for the rest of the bird's life it had the feathers of the donor Apparently it lasted indefinitely

Miller Cannon and Longmire (18) reported that if chicken skin were transplanted on a critical day after birth — I think as early as the third day — one obtained an appreciable number of "takes" But by the fourth fifth and sixth day, the number drops to 1 per cent After the 14th day no permanent takes were observed They tried marking a particular piece of skin and the feathers, and during adult life transplanting it back to the same donor However, the transplanted skin was no longer compatible

Grafflin Dr Miller, you have undoubtedly thought of this, but suppose we took dogs of the same strain and cross-anastomosed their circulation for some time before the transplant was made

Miller Dr Stanley Lang, of our laboratory, has worked out a most interesting technique He wished to find out whether the plastic bag around the transplanted kidney was really effective He developed a technique that we call pseudoparabiosis, because the idea was to have as little parabiosis as possible Dr Lang joins the skin in two rats with the minimum amount of contact He then swings the kidney over from rat A to rat B, so it lives in the new environment, but has its own blood supply We thought if there were a considerable tissue reaction, we would wrap the kidney in plastic, or modify it in other ways We have demonstrated to

our satisfaction that it is a workable technique Dr Lang has prepared one group of animals that we examined at seven days The kidney looks very healthy, and there is practically no reaction around it We are having a larger series set up We then wish to bring blood back from animal B to A, along the lines that Dr Grafflin suggested We are trying to work out a technique of getting blood shunted through the tail or some other part of the body I should be grateful for any suggestions, transferring blood continuously from one dog to another is difficult particularly if you wish to continue for several days

Luetscher Dr Miller, I wondered whether you could define the destructive process in the transplanted kidneys a little more exactly You spoke of infiltration with various phagocytic cells Do you really feel that there is any concrete evidence that this is an immunologic process that is destroying those kidneys, or do you feel that other factors are important?

Miller Are you referring now to the clinical transplants?

Luetscher Yes

Miller Surprisingly enough, we have not seen it where we expected to We have found little histologically that resembled the rejections of homotransplants in the dog In the animal there is characteristic pathology If we were to show it to an experienced pathologist, he might say, "This is definite, this looks like some kind of antigen-antibody reaction " We have not seen that in any of our patients Usually in even the badly destroyed kidneys, we were able to salvage enough tissue so that the pathologist could find a few glomeruli In none of them have we seen the outspoken allergic type of reaction In describing the case of the boy in France whose mother gave a kidney to her son, Dr Merrill mentioned that apparently this has been a human case with a rejection and histological infiltration similar to the ones observed in the dog We have been pleased, but also very puzzled, because we have not seen more evidence of it in our human transplants In fact, with the patient who lived five and-a half months, we had the impression that that kidney might have gone on for a number of months more if he had not suffered from severe hypertension Since no renal homotransplant in the dog has ever survived for a period of this length, an exact comparison is not possible

Because of the fate of skin homotransplants in humans, we have taken 120 days as about the outside limit of time for an antigen-antibody reaction Dr Merrill visited Prof P J Gaillard (19), of Leiden, Holland who has transplanted some parathyroid

He claims that as long as eight months after transplantation, he had some failures of his homografts Whether this was caused by an antigen antibody reaction, we do not know, because he has not biopsied his transplants

Luetscher I received the impression that perhaps there was some technical difficulty which might have interfered with the survival of those transplants Is that the way you feel about it, Dr Miller?

Miller We cannot draw many conclusions on the basis of ten patients In our patient who survived five and-a half months, it is very surprising that his transplant did not show more evidence of cellular infiltration, and the other things that are seen in dog homotransplants

Dock I think it is surprising that the dog homotransplants do not have an episode of proteinuria and show more glomerular reaction In Figures 28 and 29, the reaction is mostly in the hilum of the glomerulus, and that is where we see it in the Masugi nephritis That is also where the antibody appears in the Masugi lesions

Miller Yes I have been surprised, too, that there was not more reaction

Forster Have you speculated as to why you failed to obtain urine initially, right after the transplants were made? The kidney is anuric for a period of days, am I right in that?

Miller Yes, in most cases if there has been a long period of ischemia We thought that was probably governed by the same mechanism that causes acute tubular necrosis These kidneys have been ischemic, and totally deprived of oxygen for at least 200 minutes Even before death, the donor's kidneys may have been highly ischemic We have to visualize what is going on in the operating room These patients are under profound anesthesia and subjected to extensive surgery When we say 200 minutes of ischemia, we are taking the official time of death It should be apparent that there have been very long periods of ischemia in the donor's kidneys I should imagine that the pathogenesis of the renal shutdown is similar to what occurs in acute tubular necrosis

Oliver In other words, if the kidney had not been removed, but had been left *in situ* and the patient had recovered, the same thing might have happened as occurred when it was transplanted

Forster It seems to me that in this circumstance, where fluid under pressure is presented to a *filtering membrane*, especially in anoxia, one would expect high urine flows resulting from filtration and subsequent failure of the tubules to reabsorb water

Dock When the renal artery is clamped for two hours it does not begin to excrete at once It may be two or three days before it begins to pick up is that right?

Oliver Usually there is a period of delay Urine flow does not start immediately Perhaps there is some persisting vascular spasm

Forster In the absence of nerves?

Dock It is more likely that the tubular cells are all so swollen that the lumina are closed This edema can occur rapidly The tubular cells just block the outflow of any glomerular filtrate The only way we could tell is by studying the blood flow through the vascular bed in such a kidney which might be normal or quite high We could have anuria with a reasonable blood flow even if the tubules were swollen

Bull If we inject a little cyanide into a kidney the urine stops in a few minutes and the kidney swells up

Pitts Dr Dock you haven t perfused kidneys of this kind with kerosene have you?

Dock They are quite perfusible with kerosene In all these kidneys we obtain good blood flows on kerosene But that does not mean any flow coming out of the ureter because the tubules are swollen It is just like having too high a pressure in the ureter

Pitts After all how does that affect the perfusion of kerosene? It seems to me if these tubules are swollen that you will have to put a little more force behind that kerosene perfusion system of yours

Dock I think the resistance to intertubular flow is increased nearly as much as when we dilate the lumina by ureteral obstruction

Pitts I do not think I would accept that flatly

Dock You could try it on the kidney it would not take long But I think you would find the flow was down perhaps 20 or 30 per cent and the perfusibility down 20 or 30 per cent when the dog was completely anuric

Forster I have watched a lot of kidney cells die under the microscope and I have never seen kidney tissue swollen to the point where the lumen was occluded As a matter of fact in death, as you observe it directly in slices or isolated tubules the opposite seems to occur One notes a ballooning-out of the lumen rather than occlusion

Dock The ballooning is due to obstruction somewhere down below is it not?

Bull It might be interstitial fluid

Forster That is what I was thinking

Shock Is there ever protein in the urine that you obtain from these transplanted kidneys?

Miller A very small amount In the patient who went five-and a half months, I compared the transplant urine with the bladder urine, and there was a marked difference The transplant urine rarely had any casts, and only the rarest red cells, whereas we see the typical picture of chronic renal disease in the urine obtained from the bladder The proteinuria was not heavy

Dock When the first flow of urine comes, is there very little protein?

Miller There is some

Merrill I think the role of the sick patient, both from the standpoint of the donor and the recipient, is worth emphasizing in these people As you know, previous radiation of the recipient, if done at the right time, will increase the take of homografted skin Experience has also shown, that "takes" of ovarian tissue are improved if the tissue is previously refrigerated I also wondered if it might be worthwhile to consider for a moment another factor in the survival of the kidney, namely, the fact that the best survivals have been in kidneys taken from cardiacs who have been cyanotic for some period before the renal artery was clamped Perhaps we can say that the kidney has in some way "acclimated" It certainly is true that the explosive reaction that one sees occurs in the healthy kidney transplanted without any anoxia into the healthy recipient One big difference we could point out in this series is that our best results have been in "sick" kidneys transplanted into "sick" donors I think that is something that deserves emphasis

Lauson It seems to me that a good donor would be a patient who dies in heart failure due to severe, chronic, pulmonary disease This condition would provide not only a period of renal ischemia but a long period of arterial hypoxemia as well

Dock Sick donors are unfortunately not easy to find

Lauson One thing that has not been mentioned, although I am sure it has been implied, is the fact that even the best return of function in a transplanted kidney — for example, in the one in which the inulin clearance was 14 ml per minute — was much less than that expected following acute renal failure The time course of recovery of function in the transplants seems to resemble that in acute renal failure, but in the latter recovery is more than 50 per cent complete after several months of regeneration

Merrill That filtration rate of 14 ml was found 21 days after transplantation

Miller It was 28 ml, if expressed in terms of two kidneys Unfortunately at that time, infection set in We should like to know what would have happened if there had not been that period of infection However, if we can transplant a kidney that will function at 20 or 25 per cent of normal, it would still be a very useful thing to give a person who does not have any kidney function at all We compare our situation with that of research workers who re thinking of transplanting the heart or the lung If we give a erson with a 10 per cent heart a 30 per cent heart, there is not going to be much gain He would have to stay in bed and would still have all his symptoms

Do you people think that adult patients with chronic uremia are more susceptible to infection than the general run of patients?

Dock I think there is no question about that However, they have not nearly the susceptibility to infection that diabetics have

Miller That was part of the reasoning of some of our group, that the antibody mechanism was depressed or inactive

Dock I think they are a little more subject to pyogenic infections, but not to tuberculosis in the way diabetics are

Merrill The individual, in whom a renal transplant is performed, is a very ill person and I do not think there is much question that he is more susceptible to infection Of course, a good many of these eople receive ACTH or cortisone, which may be a factor in the fection

Oliver What is the route of infection in these kidneys, by the od stream or ascending from this ureter?

Iiller We are not sure

ock The bed in which the kidney was implanted has been ted in some of them

ler In the earlier transplants, we were pressed for time We ht that the period of ischemia had to be kept to a minimum, so the surgeons worked just as quickly as they could The skin was not prepared as adequately as we would have liked Also, we did not put the patients on sufficient precautions afterward, as we do now

Lawson I should like to ask whether you have dialyzed these patients in the immediate posttransplant period, in the hope that this procedure would provide a slightly more favorable environment for the transplant to "take"?

Miller A number of the patients have been dialyzed, chiefly to keep them alive I do not think there has been any correlation I

imagine it is obvious to all of us that this work could not have been done if the artificial kidney had not been developed, and if we did not have Dr Merrill's team at the Peter Bent Brigham Hospital, that could prepare these patients and also take care of their uremia when they get into difficulty immediately after the surgery

REFERENCES

1 DEMPSTER, W J Kidney homotransplantation *Brit J Surg* 40, 447 (1953)

2 SIMONSEN M BUEMANN, J, GAMMELTOFT, A, JENSEN, F, and JØRGENSEN, K Biological incompatibility in kidney transplantation in dogs I Experimental and morphological investigations *Acta path et microbiol scandinav* 32, 1 (1953)

3 SIMONSEN M Biological incompatibility in kidney transplantation in dogs II Serological investigations *Acta path et microbiol scandinav* 32, 35 (1953)

4 CARREL A La technique opératoire des anastomoses vasculaires et la transplantation des viscères *Lyon med* 98, 859 (1902)

5 ——— The surgery of blood vessels etc *Bull Johns Hopkins Hosp* 18, 18 (1907)

6 WILLIAMSON, C S Further studies on the transplantation of the kidney *J Urol* 16, 231 (1926)

7 MATSON D D Hydrocephalus treated by arachnoid ureterostomy report of 50 cases *Pediatrics* 12, 326 (1953)

8 FAVOUR C B, MURRAY, J E, WEMYSS, C T, JR, COLODNY, A and MILLER B F Serum complement levels in dogs undergoing kidney homotransplantation *Proc Soc Exper Biol & Med* 83, 352 (1953)

9 PRESSMAN D and SHERMAN, B The zone of localization of antibodies XI The *in vivo* purification of kidney localizing anti kidney antibody *J Immunol* 67, 15 (1951)

10 PRESSMAN D Radioactive tracers in the study of anti tissue antibodies *The Nature and Significance of the Antibody Response* A M Pappenheimer, Jr, Editor New York Columbia Univ Press 1953

11 KALISS N and SNELL G D The effects of injections of lyophilized normal and neoplastic mouse tissues on the growth of tumor homotransplants in mice *Cancer Res* 11, 122 (1951)

12 SNELL G D The immunogenetics of tumor transplantation *Cancer Res* 12, 543 (1952)

13 HAMILTON P B PHILLIPS, R A, and HILLER, A Duration of renal ischemia required to produce uremia *Am J Physiol* 152, 517 (1948)

14 SMITH H W *The Kidney Structure and Function in Health and Disease* New York Oxford Univ Press, 1951

15 PERSKY L and JACOB S Effect of ACTH and cortisone on homogenous kidney transplants *Proc Soc Exper Biol & Med* 77, 66 (1951)
16 MEDAWAR P B Behaviour and fate of skin autografts and skin homografts in rabbits (report to War Wounds Committee of Medical Research Council) *J Anat* 78, 176 (1944)
17 DANFORTH C H and FOSTER F Skin transplantation as a means of studying genetic and endocrine factors in fowl *J Exper Zool* 52, 443 (1929)
18 CANNON J A and LONGMIRE W P JR Studies of successful skin homografts in the chicken description of method of grafting and its application as technic of investigation *Ann Surg* 135 60 (1952)
19 KOOREMAN P J and GAILLARD P J Therapeutic possibilities of grafting cultivated embryonic tissues in man parathyroid gland in cases of postoperative tetany *Arch chir neerl* 2, 326 (1951)

ACUTE RENAL FAILURE*

GRAHAM MACGREGOR BULL
Department of Medicine
The Queen's University of Belfast
Belfast North Ireland

THE TOPIC "*Acute Renal Failure*," on which I shall speak, is a very broad term By definition it would include any condition causing acute renal failure, such as obstructions, glomerulonephritis, or even the death of the host However, in current usage, it refers particularly to tubular necrosis, and circulatory renal insufficiency The distinction between them is not, perhaps, as sharp as it might be but we regard the latter as a condition in which removal of the extrarenal factor is followed by prompt and complete return of renal function to normal

TUBULAR FUNCTION IN TUBULAR NECROSIS

The present evidence of damage to the proximal convoluted tubule rests on the finding of low Tm_G and Tm_{PAH} values, and low renal extraction of PAH They appear to show maximal abnormality early in the course of the illness and thereafter improve with time, but it could be argued that these low levels might be due, in whole or in part, to absence of glomerular function rather than actual tubular damage I think that other evidence of renal tubular damage must be sought

Despite the finding of grossly reduced values for glucose Tm for instance, it is quite rare to find glucose in the urine on ordinary clinical testing with Benedict's solution, and if glycosuria is really absent, it would indicate that the Tm_G/GFR ratio was normal or greater than normal, and suggest the possibility of complete non function of certain units Dr Oliver (1) had another suggestion at a recent Ciba conference, namely, that the absence of glycosuria might be correlated with a relative sparing of the upper part of the nephron which he had observed However, this part of the nephron is probably not uniformly spared in tubular necrosis, because Sheehan and Moore (2) found that following accidental hemor

*This work was done in collaboration with Dr A M Jockes and Dr K G Lowe at the Postgraduate Medical School London England

rhage there was often maximal damage in the neck of the glomerulus and the first small section of the proximal tubule In view of this doubt regarding proximal tubule function, Dr Kenneth Lowe has looked into the matter again * He used chromatographic methods of glucose detection, which are more delicate than Benedict's solution, and has shown that there is a pathological glycosuria almost uniformly in the oliguric phase, however, this never persisted into the early diuretic phase of the illness In support of this, Kaplan and Fomon (3) demonstrated quite a gross glycosuria in the case of mercury poisoning

By means of chromatography, Lowe has also shown an amino-aciduria of blood pattern, which occurs parallel with the glycosuria, In other words, there are not only low values for glucose Tm but so low Tm/GFR ratios This glomerulo tubular imbalance relative the proximal tubule seems to disappear with the onset of diuresis, and as osmotic diuresis does not produce glycosuria, this probably indicates that there is really proximal cell dysfunction

DYSFUNCTION IN THE DISTAL TUBULE

Two aspects of this dysfunction were discussed in an earlier paper, which I wrote in collaboration with Drs Joekes and Lowe (4) Figure 31 shows the ability to reabsorb water as shown by the creatinine and urea U/P ratios, and as you see, there is a falling off towards very low ratios indicating an inability to reabsorb water Figure 32 shows the same sort of thing for chloride reabsorption In this case, we have plotted urine/plasma concentration ratios, so that a figure of one would indicate no function and high figures would indicate reabsorption, just as in Figure 31 Here, in spite of low plasma concentrations of chloride, the ratios are low early in the course, and then improve with time In the past I have attributed these low ratios to organic cell damage in the distal tubule, but Black (5) has very rightly criticized this conclusion and suggests that both these phenomena may be due to an osmotic diuretic effect, with urea as the loading solute

The finding of isosthenuria in the oliguric and early diuretic phases, is in keeping with an osmotic effect as is this sort of linear relationship between urine volume per day and the total daily output of osmotically active material (Figure 33) However, the same results could occur from complete absence of cell function in the distal tubule or the lower part of the nephron We must look for other evidence to distinguish between the possibilities

*Personal communication

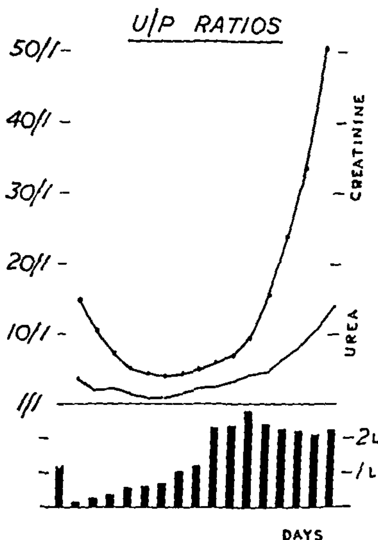


FIGURE 31 The ability of the kidney to concentrate creatinine and urea in tubular necrosis The low figures for the ratios of urine/plasma urea and creatinine indicate poor tubule function Reprinted by permission from Bull G M, Jockes A M and Lowe K G Renal function studies in acute tubular necrosis *Clin Sc* 9, 379 (1950)

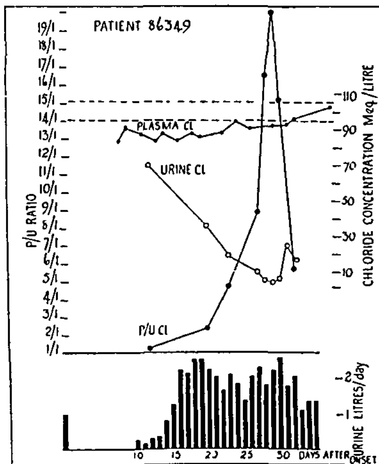


FIGURE 32 The ability of the kidneys to reabsorb chloride in tubular necrosis Reprinted by permission from Bull G M Jockes A M and Lowe K G Renal function studies in acute tubular necrosis *Clin Sc* 9, 379 (1950)

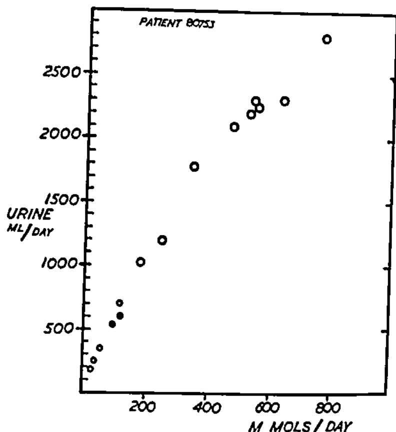


FIGURE 33 The relationship between daily excretion of total mols and urine volume per day in a patient with tubular necrosis

The chance, that there is, in fact, not as much functional damage to the distal convoluted tubule as has been thought, is raised by de Oliveira's (6) finding of a surprisingly high ammonia production in tubular necrosis in the early phase Perhaps more surprising was his finding that the urine was alkaline and yet contained ammonia

Swan He overlooks the fact that there is usually a urinary tract infection at this stage of the disease It may well be that there is ammonia in the urine, but he has not proved that it is secreted by the kidney

Bull It must have been formed in the urinary tract, because after the urine was obtained it was properly handled

Berliner I should say that experimentally we do not find much ammonia in alkaline urines

Bull This raises another point does osmotic diuresis affect the fixed base sparing mechanisms of the distal tubule? I understand from Drs Pitts and Berliner that an osmotic diuresis reduces base sparing

Berliner We have found that when the urine pH is low in the control periods, it usually rises with osmotic diuresis

Pitts This is certainly true in extreme osmotic diuresis

Bull In looking for evidence of an osmotic effect, it is unfortunate that we have no method of assessing the excreted load per nephron which would appear to determine osmotic diuresis However, I think it is fair to assume that when the blood urea is markedly raised, this will increase the excreted load per nephron, we do find a correlation between the blood urea level and the ability to re absorb water and ions

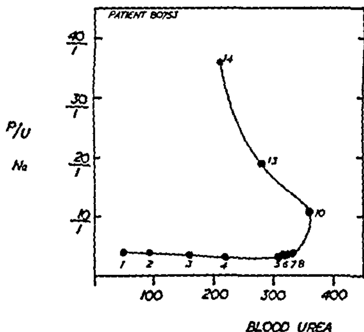


FIGURE 34 The plasma/urine sodium ratio plotted against the blood urea in a patient with tubular necrosis Numerical figures adjacent to points indicate days of illness

Figure 34 shows the concentration ratio of urine to plasma for sodium plotted against the blood urea, as suggested by Kenneth Lowe,* the figures next to the points are the days of illness There does seem to be a relationship between the blood urea level and the ability to reabsorb this ion, of a type which would be expected if we were dealing with an osmotic diuresis

Lauson Were these observations made on urines collected during 24 hours, or during short periods?

Bull They were on 24 hour urines

Lauson Was any attempt made to restrict water intake?

Bull These people were maintained on a rather low water intake

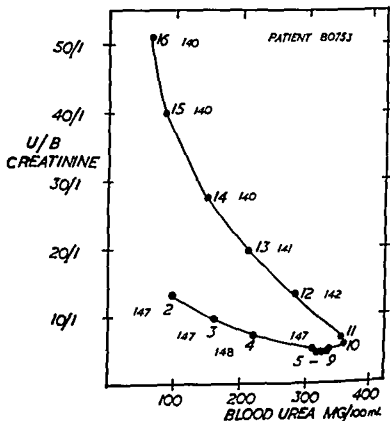


FIGURE 35 The urine/plasma creatinine ratio plotted against the blood urea in a patient with tubular necrosis Smaller numerical figures indicate simultaneous values for serum sodium concentrations (mEq/L) and larger figures indicate days of illness

*Personal communication

Figure 35 from the same patient shows the relationship of blood urea to water reabsorption as indicated by the U/P ratio for creatinine The days of illness are the larger figures near the plotted points As in Figure 34 there is a fall in reabsorption as the blood urea rises but in addition there is a change with time Later in the course of the illness the U/P ratios are higher than in the earlier stages for any given blood urea level This could be due to differences in hydration and the amount of circulating antidiuretic hormone (ADH) but at least in this patient this explanation is unlikely The smaller figures near the plotted points are the serum sodium concentrations and they are higher in the early part of the illness than the later We should therefore expect that the amount of ADH would have been higher early than late and the urine therefore more concentrated at that time However the reverse is the case

I think there are two possibilities to account for the differences in the slopes from the 2nd to the 10th day and from the 10th to the 16th day the greater reabsorption later may represent an improvement in cell function or alternatively there may be a lower filtration rate per nephron in the early diuretic phase (from the 10th to the 16th day) than in the oliguric phase (from the 2nd to the 10th day)

So far there is evidence supporting an osmotic effect A further point favoring this is the effect of dialysis Unfortunately I could find data on only one patient and in this patient the U P ratio for urea was 1 2/1 at the time that her blood urea was 260 mg per 100 ml and the next day after dialysis her blood urea had fallen to 147 mg per 100 ml with a rise in the U/P ratio to about 1 8 1

So far we have no definite evidence of tubular damage However in 2 out of 10 patients in whom we had data sufficient to plot the U P ratios against the level of blood urea there was a slightly different pattern seen Figure 36 gives one example Despite a continuing rise in blood urea there is an improvement in ability to reabsorb sodium This could indicate restoration of tubule function or a marked decrease in excreted load per nephron I think the latter is unlikely because we know that at this time glomerular filtration is improving

It seems likely that this salt and water losing state in the early diuretic phase is caused to a large extent by an osmotic diuresis but tubule damage probably does contribute to a certain extent to the phenomenon

Merrill With relation to the increased U P ratios for urea follow

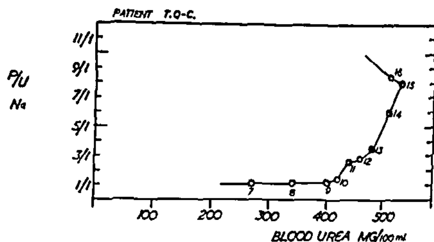


FIGURE 36 The plasma/urine sodium ratio plotted against the blood urea in another patient suffering from tubular necrosis

ing dialysis we studied that in the acutely- and chronically ill patient – that is, in the steady-state patient – and found the same thing to be true This again makes us think that it is an osmotic diuresis which occurs in these people

Bradley What percentage of filtrate do you suppose is lost?

Bull At the height of loss, probably over 50 per cent, I believe

Bradley It is questionable whether osmotic diuresis during the administration of large amounts of urea in dogs accounts for so large a loss of glomerular filtrate Is not the osmolar excretion here expressed chiefly in terms of urea output?

Bull Urea excretion yes In terms of actual milliosmols per minute excreted the amount is not at all great Even at the point where the blood urea is highest, only perhaps 600 milliosmols per day are excreted This is low in terms of the load that can be imposed in a healthy person However, as we do not know what the milliosmolar rate per nephron is, it still could be an osmotic diuresis

Dock At the time the patients have a little dextrose leakage, do they also have a potassium diuresis?

Berliner In the recovery phase, some of the patients lose quite a bit of potassium

Dock That is after the dextrose leak has been closed off is it not?

Bull Yes, before and after

Dock At any rate it is not being reabsorbed very much at that time

Merrill Dr Berliner, what was the loading solute in the osmotic diuretic experiments you spoke of?

Berliner Mannitol and sodium sulfate

Merrill Is there any difference between the two?

Berliner As I remember, they were not qualitatively different Of course, our experiments were not designed to examine that point

Swan Dr Bull, in Figure 32 you show that the urinary chloride concentration decreases over a period of three weeks or so after the onset of the diuresis, but it is still quite high as long as two weeks afterward What is the chloride intake at this time? Do you imply that this is a fixed concentration which at this stage of the disease cannot be altered by varying the chloride intake?

Bull I think it might be varied a little, not much In one patient, whom we gave zero intake of chloride the loss continued until the serum chloride was down to 55 mEq per liter

Swan That is contrary to the experience of Dr Merrill and myself Our patients on a daily intake of sodium chloride, of from 30 to 50 mEq, showed a rather rapid fall of the urinary sodium, and presumably chloride, concentration to levels as low as from 10 to 20 mEq per liter at the end of a week to ten days after the onset of the diuresis The amount of sodium excreted in each of the first few days of the diuresis was high but soon leveled off commensurate with the sodium intake There is reason to believe that there is a considerable excess of sodium and chloride to be excreted in these first few days of the diuresis but until that occurs, we do not have an opportunity to observe whether the kidney can vary to any extent, the sodium chloride concentration early in the diuretic phase

Merrill It would be extremely difficult to generalize in such situations, because the excretion rates of water and chloride depend a good deal on the condition of the patient at the time these things are done, and how one knows what his condition is in terms of sodium chloride and water load obtaining at that time I do not know I think it would be extremely difficult to generalize from patient to patient without knowing exactly what the previous balance of salt and water may have been

Bull Figure 37 gives data bearing on this point In order to demonstrate the poor tubular control over body fluid composition, we fed this patient a mineral free diet for a long period Despite the absence of minerals in her diet the urinary loss of sodium and chloride was large, up to 70 mEq per day and the plasma chloride fell to as low as 55 mEq per liter Her weight did not rise

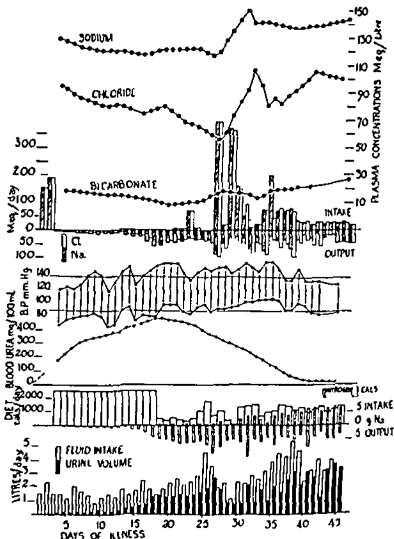


Figure 37 Data from a patient suffering from tubular necrosis showing negative sodium and chloride balance with a marked fall in serum chloride Reprinted by permission from Bull G M Joekes A M and Lowe K G Renal function studies in acute tubular necrosis *Clin Sc* 9, 379 (1950)

period that a mineral free diet was given, so that hemodilution was probably not the cause It is true that we do not yet know what the signal is for salt retention, but I think she did need salt for she later went into a strong positive salt balance

Merrill We have seen a number of patients, particularly those having difficulty with pregnancy, who at the time did not have diuresis, but during the diuretic phase that followed their anuria had been kept in negative balance in chloride without any change whatsoever in their serum level I think the load at the time the diuresis occurred might very well have influenced it Dr Bull pointed out that the patient in Figure 37 did not appear overhydrated, and perhaps that was the reason why the serum level dropped in the situation

Pitts What remained in the plasma? The sodium did not appear to fall very much

Bull The sodium was down to 115

Pitts How do you account for the difference between the sodium 155 mEq/L and the chloride of 55 mEq L?

Bull A lot of it is unexplained anion

Berliner Do you know what the carbon dioxide level was?

Bull It was down to about 12 to 15 mEq per liter

Berliner Do you mean that the bicarbonate was also low?

Bull Yes However, as often happens there was a quantity of anion, which has not been defined

Suan Dr Bull, do you believe that by varying the fluid and sodium chloride intake, you can vary the urine volume during the diuretic stage, say after the first few days of the onset of the diuresis?

Bull Yes, I think you can to a slight extent Figure 37 shows the effect of an abrupt change in fluid intake On the 25th day, one liter of fluid in excess of that calculated to maintain water balance was given There was only a modest increase in urine volume, and it took two days for the excess to be excreted, which was not a very satisfactory response to a water load

Lauson Then you reduced it a great deal by reducing the water intake?

Bull Yes Actually, what happened was this When we gave the liter of water in excess of what was needed, the patient promptly went into a state of water intoxication We then gave her sodium chloride, which improved the state of water intoxication, but from then on, we really found ourselves in trouble We started to make corrections in the blood chemistry but the faster we did so and

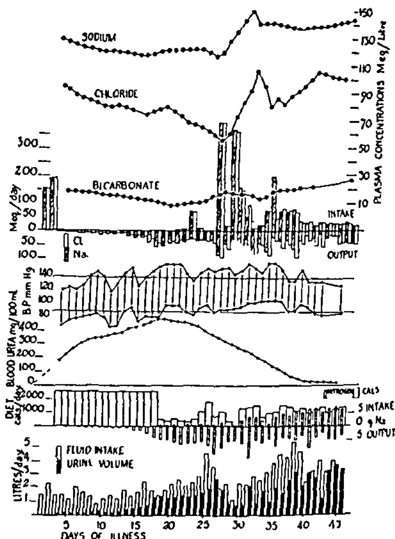


Figure 37 Data from a patient suffering from tubular necrosis showing negative sodium and chloride balance with a marked fall in serum chloride Reprinted by permission from Bull G M Joekes A M and Lowe K G Renal function studies in acute tubular necrosis *Clin Sc* 9, 379 (1950)

period that a mineral free diet was given so that hemodilution was probably not the cause It is true that we do not yet know what the signal is for salt retention but I think she did need salt for she later went into a strong positive salt balance

Merrill We have seen a number of patients particularly those having difficulty with pregnancy who at the time did not have diuresis but during the diuretic phase that followed their anuria had been kept in negative balance in chloride without any change whatsoever in their serum level I think the load at the time the diuresis occurred might very well have influenced it Dr Bull pointed out that the patient in Figure 37 did not appear over hydrated and perhaps that was the reason why the serum level dropped in the situation

Pitts What remained in the plasma? The sodium did not appear to fall very much

Bull The sodium was down to 115

Pitts How do you account for the difference between the sodium of 155 mEq/L and the chloride of 55 mEq L?

Bull A lot of it is unexplained anion

Berliner Do you know what the carbon dioxide level was?

Bull It was down to about 12 to 15 mEq per liter

Berliner Do you mean that the bicarbonate was also low?

Bull Yes However as often happens there was a quantity of anion which has not been defined

Swan Dr Bull do you believe that by varying the fluid and sodium chloride intake you can vary the urine volume during the diuretic stage say after the first few days of the onset of the diuresis?

Bull Yes I think you can to a slight extent Figure 37 shows the effect of an abrupt change in fluid intake On the 25th day one liter of fluid in excess of that calculated to maintain water balance was given There was only a modest increase in urine volume and it took two days for the excess to be excreted which was not a very satisfactory response to a water load

Lawson Then you reduced it a great deal by reducing the water intake?

Bull Yes Actually what happened was this When we gave the liter of water in excess of what was needed the patient promptly went into a state of water intoxication We then gave her sodium chloride which improved the state of water intoxication but from then on we really found ourselves in trouble We started to make corrections in the blood chemistry but the faster we did so and

the more normal the blood chemistry became the worse the patient became

Swan Can we reduce the urine volume within the first week say of the onset of the diuresis if we have reduced the load of solute to be excreted?

Bull Yes

Swan In other words have the statements in the literature to the effect that there is an obligatory polyuria of several liters per day been made as a result of not having attempted to restrict sodium and water?

Bull No *The way in which the fall in urine volume on water restriction in early diuresis comes about is* I think circulatory The patients continue to pass urine until they become dehydrated and a circulatory insufficiency develops in addition to their other trouble We have one patient who actually died because of that

Lawson Is there an analogy with far advanced nephritis in this situation? In that disease the tubules no longer have much variability or selective capacity left so when urine output and solute excretion vary according to intake this presumably occurs on a circulatory basis

Merrill Dr Swan in some of the water loading experiments you did did you not show that administration of 1 500 to 2 000 ml of water is reflected in the urine volume over the subsequent 24 hours or so but not immediately? It is difficult for me to believe that that amount of water administered slowly in a patient who maintained normal blood pressure and well being during that period of time could be entirely on the basis of circulatory readjustments I feel that the blunted response is a little more pertinent in view of the unchanging clinical situation

Swan We studied a patient on the ninth day after the onset of the diuresis during which the daily urinary volume exceeded 400 ml The oliguric period in this patient had lasted 19 days On the ninth day of the diuresis after body weight had become stable doubling the water intake from two to four liters for a two day period was associated with a commensurate increase in urine volume The patient suffered no ill effects When fluid intake was again restricted to two liters daily urinary volume decreased (7)

Merrill Were the solutes excreted the same?

Swan The patient was on a constant sodium chloride intake of from about 30 to 40 mEq per day There was some increase in sodium excretion during that time Marked and prolonged polyuria during the diuresis is partially an artefact due to the physicians

attempt to maintain body weight and replace urinary loss of electrolytes and water, and his neglect of the need of the patient to lose water and sodium chloride which has accumulated as the result of catabolism and excessive intake during oliguria Moderate restriction of water and salt with the onset of the diuresis results in prompt weight loss, but not in the patient becoming clinically dehydrated If the patient, at any point after this acute weight loss, is allowed a more liberal diet, the weight does not change appreciably

Bull The case I quoted earlier, of the patient who actually ran himself down into a state of circulatory insufficiency, shows that excessive losses can occur

Swan I wonder whether it occurs unless water intake is restricted to the point where the solute load is greater than the ability of the kidney to excrete solutes without depleting body water At this stage the kidneys cannot excrete a concentrated urine of course If we increase the sodium chloride intake, or if we fail to restrict it, then there will be depletion of body water

Berliner If the kidneys cannot concentrate or dilute the urine, how can they get rid of the extra water without more sodium to go with it?

Swan Within a week or so of the onset of the diuresis they can excrete a more dilute urine

Berliner Does it not depend on what stage we are talking about?

Swan An opportunity to study this in the first few days after the onset of the diuresis is not afforded, but when excess water and sodium have been excreted, urinary volume and sodium concentration can be altered considerably by varying the intake

Merrill In your experience, is it practical to conserve sodium in this state?

Swan Yes

Merrill There is a question whether the ingestion of two liters of water will influence the dynamics of the kidney enough so that there will be a marked change in urine volume

Doc' [illegible] when the patien [illegible] and with blood [illegible] ded house officer does a concentration test with a low fluid intake The blood urea begins to climb with only this one insult, and even if dehydration is started again, it takes a while to correct the condition It is surprising in these patients, how one concentration test will upset the situation

They have a little decrease in their food and salt intake, and an

increase in their own protein breakdown, but it upsets the whole mechanism, so I personally see no point in ever allowing a concentration test to be done on patients with hypertension if it is known that their blood urea has begun to rise We do not learn anything as clinicians by doing concentration tests Dr T Addis used to do the opposite Occasionally he would precipitate a bout of acute pulmonary edema during the opposite phase of his concentration dilution test I think everybody who has made frequent tests on the effects of sudden changes in water load in patients with fixed specific gravity, has run into trouble, both in the acute and chronic stages We can produce acute renal failure by 24 hours of rigid restriction of water intake

Merrill As I said before, it probably depends on the state of hydration of the patient at the time the determinations are made

Swan If we look on the excessive output of water as the result of an osmotic diuresis, do you suppose that by varying the sodium chloride intake we could perhaps vary the U/P ratio of urea considerably?

Bull Not markedly For instance, in the same patient shown in Figure 37, the marked change in NaCl intake on the 26th to the 28th day was not associated with much change in U/P urea That a diuresis can occur even in the face of dehydration is shown in another patient who developed anuria following an abortion She remained at home, drinking very little, and came to us on the 12th day very dehydrated Instead of giving her a lot of fluid, we merely gave one liter in excess of her urinary volume per day, and despite continuing dehydration, as shown by a high hematocrit and plasma specific gravity, she had a diuresis In fact, I think there is an obligatory loss of water and salt in the early diuretic phase and that this can create trouble for the patient — probably circulatory trouble

Merrill If we postulate that this is an osmotic diuresis and there is unanimous agreement, as Dr Bull has pointed out, certainly under those conditions there is an obligatory loss of salt and water I think that if a patient is extremely dehydrated when this begins he will find himself in trouble If not, he probably will not I wonder if that is not the reconciliation of these two points of view?

Dock If patients are run on your dialyzers, do you see this phenomenon?

Swan We do not remove edema or extracellular fluid with dialysis

Dock No but we take the urea out, which is an osmotic load

is it not? This is the usual cause of the osmotic diuresis, and if the blood urea is brought down close to normal by an artificial kidney, then this phenomenon should not be seen at all

Merrill I do not think it is quite as simple as that There is no question but that it varies the urine volume, but it does not completely obviate the diuresis occurring To some extent, perhaps, that is due to the fact that few of these patients have been dialyzed during the diuretic period, or just before it

Dock And diuresis occurred, even though their blood urea had been brought down?

Merrill Yes But there is such a tremendous variability in the urinary output that again I do not see how one can compare from patient to patient

Suan Dr Luetscher, I should like to ask what you believe to be the mechanism of the hyperchloremia sometimes seen in this stage of the disease, since you are the one who first called attention to this phenomenon

Luetscher We made only a few observations on these patients In most instances, intoxication with a sulfonamide appeared to be responsible for the acute renal injury There was nothing characteristic about the anuric phase, although some patients received more fluids than we would give today to an anuric patient These patients doubtless had a high total body content of sodium and water In the early diuretic phase, the patients put out large volumes of urine containing very little sodium or chloride The serum levels of sodium and chloride rose to normal and then to abnormally high levels, associated with loss of edema and progressive dehydration The blood urea level started to fall with diuresis, but rose again with dehydration

These patients had an unusually high water requirement Five to six liters of sodium free fluids were needed each day in order to rehydrate the patient and dilute the extracellular electrolytes to normal levels

I am not sure that I understand, in any fundamental terms, how these patients differ from the average patient who tends to be a salt loser Our patients were water losers, but their U/P ratios for chloride and sodium fell to very low levels almost from the start of the diuretic phase

Burnett I think the point you made about the previous salt loading is important In our experience the ones in whom diuresis was associated with hyperchloremia received quite large quantities of salt before the diuretic period This seemed in some way to set the

stage for retention of sodium and chloride in excess of water I have no idea what the mechanism is

Luetscher It is almost certain that the tubule is not responsible at this stage as far as the regulation of the body fluids is concerned The early diuretic phase seems to be the result of a set of mechanical processes which are very poorly responsive to the fluid and electrolyte loading state of the patient at that time

Swan You say it is almost certain There is considerable doubt in my mind After all if you restrict either water or sodium in these patients their urinary volume decreases or their sodium concentration falls On a constant water intake if sodium intake is increased the urinary concentration of sodium increases considerably If water intake is increased and sodium intake kept constant urinary volume increases considerably and sodium concentration falls

Luetscher But only at the expense of more marked changes in the concentration and volume of body fluid than would produce the same changes in urine in the normal person under the same circumstances

Bull Admittedly there is some regulation but it is all so blunted that it allows a state of affairs to develop such as that shown on Figure 37 where the patient had a serum chloride of 55 mEq You could not do that in the normal person

Swan By changing conditions the clinician could vary the composition of the urine even as early as a week or less after the onset of the diuresis if there were not this excess amount of water and sodium to be excreted

Pitts I seem to detect a slight difference in patients in Britain California and Boston I wonder if further discussion of this situation is really very profitable because therapy may provide us with an answer What Dr Bull advises for therapy may well explain what differences he observes in response to therapy I rather imagine that the treatment in the British Isles and Boston may have been somewhat different which would account for some of the differences in results

THE TREATMENT OF TUBULAR NECROSIS

Bull This subject has received a good deal of attention in the last ten years and as a result the mortality has fallen from between 60 and 90 per cent to about 20 or 30 per cent Probably the largest single factor has been a more general appreciation of the importance of the water and salt balance and whether the treatment used has

been dialysis or dietary or both does not seem to make much difference to the end result Personally I prefer the conservative type of management rather than dialysis simply because it is easier and I think that almost all the disturbances in the electrolyte pattern that one meets in these patients can be corrected by appropriate conservative methods In any event I think that the fall in mortality that has occurred has been achieved by relatively simple attention to water and electrolyte balance and that any further material improvement will depend on attention to other factors The most important of these other factors are the presence of associated injuries or illnesses and particularly the factor of infection

To illustrate this I propose to review what I believe to have been the causes of death in the patients seen by Dr Jockes Dr Lowe and myself The first group of patients to consider are 39 who were treated conservatively along the lines indicated in a paper published in 1949 (8) Basically the treatment was bed rest with the feeding by intragastric drip of a synthetic diet containing 400 gm of glucose 100 gm of peanut oil and water to one liter The total water in a liter of this diet assuming that all the fat and carbohydrate are metabolized is approximately 810 ml

The mean duration of oliguria (less than 1 000 ml of urine per day) was 10 4 days with a standard deviation of 5 7 days There were 7 deaths a mortality of 18 per cent The causes of death are shown in Table IX

I believe that infection played a major role in the death of four of these patients However the importance of infection was even more striking in the second series of 54 patients who were treated by a number of methods Not all were under our care but we saw them either in our own hospital or elsewhere There were 17 deaths and in Table X I have listed what I consider to be the principal causes In ten out of the 17 patients infection was probably the most important factor

The nature of the infections is shown in Table XI Five patients had bronchopneumonia and in four of them the infection developed during the period of oliguria Of the three patients with septicemia one developed this condition from a pelvic infection and in the other two it followed and was probably caused by infection during dialysis Two patients had peritonitis This problem of infection was one of the main difficulties we had with the original Kolff machine During dialysis the bath containing glucose among other

TABLE IX

Patient	Diagnosis	Number of Days after Onset at which Death Occurred	REMARKS
1	Abortion	9	Oliguric form onset Fulminating C *Septique* infection in pelvis Death from infection
2	Abortion	15	Pelvic infection partially controlled by antibiotics Flared up in early diuretic phase Death from infection
3	Incompatible transfusion	17	Gastrectomy Incompatible transfusion Paralytic ileus Burst abdomen Bronchopneumonia Death from infection
4	Incompatible transfusion	18	Abdominoperineal resection Incompatible blood transfusion Diuresis 17th day, but developed severe diarrhea collapsed and died Autopsy showed widespread metastases Circulatory death
5	Cortical necrosis	9	Preeclamptic toxemia Concealed accidental hemorrhage Hypertension persisted Death from pulmonary edema
6	Sulfonamide sensitivity	23	Pneumonia Given sulfonamides Anuria Pneumonia did not resolve and developed severe ascending pyelonephritis from indwelling catheter Death from infection
7	Abortion	28	Fall in serum K in early diuretic phase Paralysis and coma failed to respond to K Death from electrolyte disturbance

TABLE X

Main Cause of Death	Number of Patients
Infection	10
Disturbances of water and electrolyte balance	6
Hemorrhage	1

TABLE XI

Type of Infection	Number of Patients
Pneumonia	5
Septicemia	3
Peritonitis	2
Pyelitis*	1

*This patient also had pneumonia

things was warmed to 37° C and acted as an excellent culture medium

All of these infections were resistant to penicillin and usually to streptomycin also The commonest infecting organism was the *Staphylococcus* We invariably gave all these patients one mega unit of soluble penicillin per day which in anuric or oliguric subjects results in very high blood levels We also gave streptomycin and sulfonamides in suitably reduced doses in some cases but at the time we treated these patients we did not have available in London any of the other antibiotics which could be procured now

The ill effects of infection obviously include a tendency to upset mineral and water balance and nullify one's attempts at protein sparing so that the distinction between deaths from infection and from "the uremias" is not always clear However patients do die of infection with apparently normal blood chemistry at least with respect to electrolytes and I think that any further significant lowering of mortality will depend more on better treatment of infection rather than any further refinement in methods of achieving mineral and water balance What are your views on this Dr Merrill?

Merrill I entirely agree with you that infection is the cause of

death in many of these patients On the other hand, what pr poses them to infection? Any one of us who had contact with sort of organism these patients had, would probably not die of infection and I think we all know that these people, before th were infected must have been critically ill from a condition wh we usually label uremia Uremia' certainly predisposed them t infection and perhaps made the difference between their susceptibil ity and their ability to resist the infection As Dr Bull has also pointed out, infection *per se* does obviate our attempts to spare protein

One of the things that we believe to be important in the use of the artificial kidney, is the amelioration of the one factor we could get at during the anuric phase, and that is the uremic syndrome We do not know what it is, but we do know, and it is well docu mented that a patient acutely ill from the chemical toxicity of uremia, will, following dialysis, be alert and able to sit up and move around Good surgical care is one of the things that will help the patient combat infection In this situation, we feel that the artificial kidney does have some use However, we believe and Dr Bull does also, that it rarely influences the mortality in any other way except in that particular fashion

With respect to hemorrhage or infection occurring as a result of dialysis I think Dr Bull and I are talking about two different things There is a great difference between the operation of the Kampen machine and the machines that have been built in this country I do not think we would continue if we had to work with the original Kampen model

I wonder about the high fat diet As Dr Bull has pointed out we know that the majority of these patients were in difficulty be cause of mistakes in therapy, some of which could have been pre vented A good many of them were previously healthy people who had become subject to trauma or acute surgical procedures and as a result of that the problem arose In this case, it is extremely difficult to influence, by caloric intake, the protein catabolism during the first week or ten days following the acute trauma Most of these patients have a good store of body fat and they can burn that as well as the fat that is given to them by mouth They may do that as Dr Moore (9) has shown at the rate of from 3 000 to 3 500 fat calories per day I do not think there is anything to be gained by adding another 2 000 fat calories by mouth Engel (10) has shown theoretically, that in this situation fat and protein will not obviate that condition but glucose will For that reason we have concentrated on glucose

In addition there are the many obvious objections that I am sure Dr Bull has thought about to forced feeding with a diet which unquestionably is distasteful and which may cause diarrhea vomit ing and electrolyte disturbances I think both Dr Bull and I would agree that these considerations are more important than elevation of the nonprotein nitrogen and that in our experience both from the theoretical and practical standpoint fat has not seemed a very effective adjunct to the treatment of these patients in an anuric state We prefer to use glucose which I think has a sound theoretical basis We administer it in a 50 per cent solution by a plastic catheter placed high in the brachial or femoral vein This has the advantage of enabling us to give a large number of carbohydrate calories in an extremely small volume of water and as it is a con tinuous process it is the most effective method of caloric administra tion It also gives us a constant drip to which anything can be added as therapy dictates After some experience we have given up high fat diet as a form of therapy during the acute period Our results have not changed much however they have probably improved a little bit

Pitts How many calories would you give in the form of 50 per cent glucose?

Merrill That depends upon what we think the fluid intake should be We give as many calories as can be administered by a 50 per cent solution the total amount depending upon the volume of fluid that we think ought to be administered

Pitts Is that the total fluid intake?

Bull That is the total fluid intake in an anuric patient which is 600 ml per day If the patient is passing urine a volume of fluid equal to that urine is added to the next day s intake

I have no strong feelings about the fat in the diet and in fact am gradually reducing the quantity Lately I have been giving 50 gm per day and perhaps I shall eliminate it entirely The carbohydrate is much more important and I think that a very high carbohydrate intake is indicated Some people believe that a high carbohydrate intake is not necessary in order to produce adequate protein sparing That is possibly true but a very high carbohydrate intake has a further advantage in that it keeps the serum potassium low and even causes it to fall

Burnett Do you think there is good evidence that increasing the carbohydrate intake above 100 gm per day suppresses protein metabolism or potassium accumulation?

Bull I have observed a completely anuric patient in whom the

serum potassium fell and stayed down for a matter of five or six days

Merrill I should certainly agree with that The work showing decreasing increments of protein sparing with glucose administration of over 100 gm was done with normal young men who were resting and I think it is an entirely different situation from that of compound fracture and trauma injury In the latter case increasing the glucose may be important It certainly has been our clinical experience and Dr Bulls also that the incidence of potassium intoxication which we used to think was a very frequent cause of difficulty has decreased tremendously since we started the administration of 50 per cent glucose 24 hours a day

Miller Is it possible that the massive administration of glucose is preventing the cure of the infections that cause the death of some of these patients?

Bull I do not know I think most of that glucose is being stored as glycogen and that is why the serum potassium does not rise Blood sugars do not tend to run high

Dock Four hundred grams of glucose would not be very different from what we are getting in carbohydrate every day and most of us have not developed infections yet However these patients have a higher metabolism than we have many of them are febrile

Miller They also have many more active bacteria

Berliner How much glucose does the average patient receive? Is any additional water given?

Merrill These steady state patients usually receive about 400 ml of a 50 per cent glucose solution

Dock Only 200 gm then

Pitts So that would be approximately 300 ml of water per day That is assuming about half a ml of water of oxidation per gm of glucose

Berliner That is all the water you give the patient?

Merrill Yes

Dock The tip of the polyethylene catheter has to be in a very large vein when a 50 per cent glucose solution is administered

Merrill As has been pointed out infection in these people is a major problem particularly in the use of the intravenous catheter It depends entirely upon the care with which it is put in place In the particular series which I have observed there has been very little infection We usually do not leave the catheter in for more than five or six days and then shift it to the other side if that is

feasible On the other hand when it is put in by some of the house staff who are inexperienced in the procedure the incidence of infection or phlebitis, is almost universal

Dock Is the catheter inserted at the foot in the femoral artery, or in the arm?

Merrill A small polyvinyl catheter is put through the saphenous, and threaded to the iliac Of course another advantage is that when one provides fluid over a 24 hour period it does not immobilize the patient The incidence of bronchopneumonia that Dr Bull mentioned may also be an important factor particularly in the elderly patient

Dock The tubes go in veins and not down the esophagus to minimize the risk of aspiration pneumonia?

Merrill That is right That too has been a problem for us I do not imagine that Dr Bull keeps tubes in for a long period of time but a good many of these patients who are critically ill bleed from the nasopharynx and throat and that is a real problem if a tube is in for a long period of time or even if it is constantly being put in and taken out

Dock This really requires good surgical threading of the polyethylene tube You use the saphenous rather than the arm vein?

Merrill You can use an arm vein

Dock Then you put the tip into or at least past the innominate vein so it is practically in the vena cava?

Merrill No we have been able to do it by getting up into the brachial vein

Dock I should think you would get thrombosis

Berliner The solution does not come out of the tube very fast

Merrill When you administer only 400 ml of fluid which is 50 per cent glucose per day you do not inject a lot of fluid at any one time

Lawson I should like to ask whether you have had any experience with the administration of androgens during this period That would seem to be a logical step

Merrill We routinely use testosterone propionate in these people and there is a tremendous amount of evidence in the experimental literature, why we should As you may realize a controlled study is almost impossible in this situation but I think it is the feeling of most of us in Boston working in different hospitals and without being able to document it that it probably is a useful and worth while adjunct Certainly it does no harm and may do some good

serum potassium fell and stayed down for a matter of five or six days

Merrill I should certainly agree with that The work showing decreasing increments of protein sparing with glucose administration of over 100 gm was done with normal young men who were resting and I think it is an entirely different situation from that of compound fracture and trauma injury In the latter case increasing the glucose may be important It certainly has been our clinical experience and Dr Bulls also that the incidence of potassium intoxication which we used to think was a very frequent cause of difficulty has decreased tremendously since we started the administration of 50 per cent glucose 24 hours a day

Miller Is it possible that the massive administration of glucose is preventing the cure of the infections that cause the death of some of these patients?

Bull I do not know I think most of that glucose is being stored as glycogen and that is why the serum potassium does not rise Blood sugars do not tend to run high

Dock Four hundred grams of glucose would not be very different from what we are getting in carbohydrate every day and most of us have not developed infections yet However these patients have a higher metabolism than we have many of them are febrile

Miller They also have many more active bacteria

Berliner How much glucose does the average patient receive? Is any additional water given?

Merrill These steady state patients usually receive about 400 ml of a 50 per cent glucose solution

Dock Only 200 gm then

Pitts So that would be approximately 300 ml of water per day That is assuming about half a ml of water of oxidation per gm of glucose

Berliner That is all the water you give the patient?

Merrill Yes

Dock The tip of the polyethylene catheter has to be in a very large vein when a 50 per cent glucose solution is administered

Merrill As has been pointed out infection in these people is a major problem particularly in the use of the intravenous catheter It depends entirely upon the care with which it is put in place In the particular series which I have observed there has been very little infection We usually do not leave the catheter in for more than five or six days and then shift it to the other side if that is

feasible On the other hand, when it is put in by some of the house staff who are inexperienced in the procedure, the incidence of infection, or phlebitis, is almost universal

Dock Is the catheter inserted at the foot, in the femoral artery, or in the arm?

Merrill A small polyvinyl catheter is put through the saphenous, and threaded to the iliac Of course another advantage is that when one provides fluid over a 24 hour period it does not immobilize the patient The incidence of bronchopneumonia, that Dr Bull mentioned, may also be an important factor, particularly in the elderly patient

Dock The tubes go in veins and not down the esophagus, to minimize the risk of aspiration pneumonia?

Merrill That is right That too, has been a problem for us I do not imagine that Dr Bull keeps tubes in for a long period of time, but a good many of these patients, who are critically ill, bleed from the nasopharynx and throat, and that is a real problem if a tube is in for a long period of time, or even if it is constantly being put in and taken out

Dock This really requires good surgical threading of the polyethylene tube You use the saphenous rather than the arm vein?

Merrill You can use an arm vein

Dock Then you put the tip into, or at least past, the innominate vein, so it is practically in the vena cava?

Merrill No, we have been able to do it by getting up into the brachial vein

Dock I should think you would get thrombosis

Berliner The solution does not come out of the tube very fast

Merrill. When you administer only 400 ml of fluid which is 50 per cent glucose, per day you do not inject a lot of fluid at any one time

Lauson I should like to ask whether you have had any experience with the administration of androgens during this period That would seem to be a logical step

Merrill We routinely use testosterone propionate in these people, and there is a tremendous amount of evidence, in the experimental literature, why we should As you may realize a controlled study is almost impossible in this situation, but I think it is the feeling of most of us in Boston, working in different hospitals and without being able to document it, that it probably is a useful and worthwhile adjunct Certainly, it does no harm and may do some good

serum potassium fell and stayed down for a matter of five or six days

Merrill I should certainly agree with that The work showing decreasing increments of protein sparing with glucose administration of over 100 gm was done with normal young men who were resting, and I think it is an entirely different situation from that of compound fracture and trauma injury In the latter case, increasing the glucose may be important It certainly has been our clinical experience, and Dr Bull's also, that the incidence of potassium intoxication, which we used to think was a very frequent cause of difficulty, has decreased tremendously since we started the administration of 50 per cent glucose 24 hours a day

Miller Is it possible that the massive administration of glucose is preventing the cure of the infections that cause the death of some of these patients?

Bull I do not know I think most of that glucose is being stored as glycogen, and that is why the serum potassium does not rise Blood sugars do not tend to run high

Dock Four hundred grams of glucose would not be very different from what we are getting in carbohydrate every day, and most of us have not developed infections yet However, these patients have a higher metabolism than we have, many of them are febrile

Miller They also have many more active bacteria

Berliner How much glucose does the average patient receive? Is any additional water given?

Merrill These steady-state patients usually receive about 400 ml of a 50 per cent glucose solution

Dock Only 200 gm, then

Pitts So that would be approximately 300 ml of water per day That is assuming about half a ml of water of oxidation per gm of glucose

Berliner That is all the water you give the patient?

Merrill Yes

Dock The tip of the polyethylene catheter has to be in a very large vein when a 50 per cent glucose solution is administered

Merrill As has been pointed out, infection in these people is a major problem, particularly in the use of the intravenous catheter It depends entirely upon the care with which it is put in place In the particular series which I have observed, there has been very little infection We usually do not leave the catheter in for more than five or six days and then shift it to the other side, if that is

to intravenous feeding Did you run into any difficulties with distention and vomiting Dr Bull?

Bull Yes In patients like that who had ileus were vomiting excessively, or in whom the gastrointestinal route for feeding was contraindicated we did almost exactly what Dr Merrill suggested we injected 50 per cent glucose usually through a catheter passed via an arm vein into the superior vena cava If the vein did not become inflamed which it usually did not we would leave it there for a long period even up to a fortnight if necessary A curious thing happens if death occurs and a postmortem is performed a vein developing within a vein is observed The catheter becomes coated with thrombus and a certain amount of endothelialization takes place as well

Dock Does this occur in two weeks?

Bull Yes

Merrill What material did you use for your catheter?

Bull Polyethylene

Dock Does this begin at the site where the catheter is introduced?

Bull At that site there is no parallel lumen but higher up where it enters a big vein there appears a vein within a vein

Merrill Two points which have been made during the previous discussion might be pertinently raised at this moment they will certainly create a little dissension One is the problem of treating congestive heart failure or at least acute pulmonary edema, in these patients and the second is as Dr Bull points out correction of the abnormal electrolyte patterns Perhaps I might rephrase these problems in two questions First do you think that the pulmonary edema that occurs in these patients is a result of increased hydration hypertension or both? And if so do you think that digitalis is as effective in these cases as in other forms of congestive heart failure? Second do you think that in the absence of demonstrable losses of electrolyte or overhydration with excess water low serum sodium values should be corrected and brought back to normal with the administration of hypertonic sodium solution?

Bull I do not think that the cardiac failure is due to hypertension in most patients It occurs without it and as I said earlier diastolic pressures of over 100 mm Hg are rarely observed Overhydration is probably important but it can occur without overhydration I do not think that this is cardiac failure of the ordinary type because the circulation time and the cardiac output are usually not abnormal and digitalis seems to be ineffective in treatment

Breed Do you have any data on the use of ACTH or cortisone during the early stages of anuria Dr Merrill?

Merrill Yes we do ACTH and cortisone after the anuric period has occurred of course is contraindicated for obvious reasons It has been suggested that because the early pathological lesion is one in which there is edema and perhaps some degree of inflammatory response ACTH or cortisone might obviate that We had a chance observation in a young man who had myoglobulinuria which made us think that this was not valid During an exercise tolerance test he was given steroid to see if cortisone would prevent the occurrence of the condition However during the period when he was being given a rather large dose of cortisone this man became anuric and remained so for some days thereafter Thus I think cortisone has very little value

Breed I think we observed in one or two cases of anuria who were also receiving ACTH that the plasma potassium level rose rather rapidly

Swan Dr Bull what was the nature of the electrolyte disturbances which caused death in the patients you cited?

Bull In the first group all of whom we treated ourselves there were three deaths that might be classified as due to electrolyte and water disturbances The fourth patient developed very severe diarrhea and rapid general circulatory collapse The fifth died of pulmonary edema but I think this was partly due to hypertension and not a simple overhydration phenomenon The sixth patient was the only one in this group in whom an electrolyte disturbance alone was probably responsible for death Her serum potassium fell in the early diuretic phase and there was paralysis electrocardiographic change and stupor Administration of potassium sufficient to raise the serum potassium to slightly supernormal levels did not appear to be effective and she died why we do not know

In the second group the problem was usually one of straight water and salt overload and death was usually from pulmonary edema In neither group was hyperpotassemia much of a problem in fact in the early diuretic phase hypopotassemia was much more important

Luetscher You mentioned one patient in whom ileus occurred We have seen a number of these patients often with some intra abdominal disease which led to their acute renal failure We have been impressed with the difficulties of supplying food and fluid to the anuric patient via the gastrointestinal tract This has occurred with sufficient frequency so that we have gone back almost entirely

sodium losses and excess intake of water may take a tremendous dive This is not amenable to correction with hypertonic therapy If the cardiac output improves the patient recovers and the serum sodium will rise in spite of a negative balance of sodium I think therefore there are situations in which that should not be corrected simply because the serum level is abnormal

On the other hand if it is the result of a sodium depletion or excess administration of water I think there is some rationale for

When we are uncertain we approach it much as Dr Burnett has done with extreme caution we use small amounts and administer it slowly If it appears to be doing well we continue but otherwise we stop altogether However I do think one should attempt to make this decision in advance it requires experimentation

Bull We are probably in agreement there but I think it is undesirable to treat just the cosmetic appearance of the electrolyte pattern

Dock Are you sure that some of the unaccounted for nonprotein nitrogen in these people is not taking the place of chloride?

Bull Something is

Dock There is a lot of unaccounted for nonprotein nitrogen It is neither creatinine nor urea There may also be a base in that material as well as acid is that not so? Sodium might decrease because there is now more organic base than in normal people

Bull Yes there is a possibility of that Mathé (11) is making measurements of freezing point depressions on the plasma and also electrical conductivity and when he adds up all the things he has measured there is still a gap on both the base and the anion side which is unaccounted for He thinks that water intoxication symptoms can be correlated with a fall in what he calls "effective extracellular molarity"

I should like to ask the physiologists a question It seems to those of us who are treating these patients that the osmotic effect may be quite an important one In the trouble they run into in the early diuretic phase how far is an osmotic effect responsible and how can we define an osmotic diuresis?

Berliner What I mean by "osmotic diuresis" is the diuresis that results from the filtration of solute which cannot be reabsorbed by the tubules and which carries with it into the urine a certain amount of water and other solutes as a result of the osmotic effect within the tubule

Now as to whether the situation in recovery from

The second question, that of the correction of electrolyte disturbances, is, I think, important We have been impressed by the fact that very gross changes in chemistry may occur without any symptoms or signs I do not think that attempts at improving the "cosmetic appearance" of the electrolyte pattern are always wise Figure 37 illustrates this point also Up to the 25th day the patient was reasonably well, listening to the wireless, reading and so on and that in spite of a serum sodium of 115, and a serum chloride of 55 mEq per liter On the 25th day we gave her two liters of water in excess of her previous day's urine volume, instead of the usual one liter She developed a state of water intoxication This was treated by the administration of about 375 mEq of NaCl, with improvement Soon afterward, however, she became confused, developed twitching, and was obviously worse We then attempted to correct rapidly all the electrolyte disturbances we could detect The more normal the electrolyte pattern seemed to be, the worse she became clinically, and in the end we just let nature take its course and she recovered This, and a few similar experiences, have made us think that as long as the patient is symptom free, it is better to leave him alone, or if any correction is attempted, to do it very slowly

Burnett We would take a different view on this When the patient comes to us with hyponatremia, often as a result of poor treatment, we usually proceed, especially during the oliguric phase, on the basis that there is some evidence that hyponatremia itself may compromise renal function When the patient is first seen, we frequently do not know what we are dealing with In administering hypertonic saline, we have not experienced the unfortunate consequences which have been reported We are not at all sure it does any good in many instances, but we are not convinced that it does any harm

Merrill As in the administration of water and electrolyte during the diuretic period, we have to consider the situation with which we are dealing, and as Dr Burnett mentioned, if we have a patient with difficulties as a result of mismanagement, obviously something has to be done about it However, we are also familiar with cases where management has been extremely good, and in spite of that the patient shows a depression of serum sodium levels This is seen, of course, in the chronic cardiac patient, in malnutrition, and also in many forms of disease It is seen very characteristically in the cardiac patient with a normal serum sodium who undergoes valvulotomy, and in that patient the serum sodium, in the absence of

would not disturb the plasma osmolarity very much By giving increasing doses, we could produce a flow load curve in each case

Pitts You do not know how it is distributed among the population of nephrons

Lauson True, such a curve would not give any information on that point

Merrill The other problem is that the functioning nephron population probably changes a great deal from day to day in recovery from acute renal failure

Pitts Of course, if there were any way to do it we could measure it during illness, and again after the individual had recovered But I do not see how it could be measured

Lauson To return to the definition of osmotic diuresis it is obvious to most of us, I think that any urine flow has an osmotic component This is true even in the midst of maximum water diuresis By definition, as Dr Berliner says any time that solute is excreted, water will also be excreted In this sense there is some osmotic diuresis in all urine flows

Luetscher This concept gets a little thin when the urine is hypotonic, does it not?

Berliner No, there can be a hypotonic urine and an osmotic diuresis

Bradley That is usually the case

Berliner I think what Dr Lauson has said is true but I do not mean quite that when I say 'osmotic diuresis It is hard to draw the line as to where one stops and the other begins but when I say "osmotic diuresis' I am usually thinking of the excretion of enough solute to modify the excretion of other solute

Oliver What other form of diuresis might one contrast with osmotic diuresis?

Berliner The only diuresis that is not osmotic diuresis in that sense, is water diuresis For instance if we give a mercurial diuretic we are presumably interfering with the transport of some solute As a result, we can convert, say chloride to the equivalent of mannitol, instead of something which can be easily reabsorbed

Merrill Is there any way that one can distinguish between possible osmotic diuretic effect in this situation and the result simply of failure to readsorb water by lack of pitressin effect? What is the action of pitressin in an individual given a large amount of mannitol?

The point that seems pertinent here is how much of this osmotic diuretic effect is just that, and how much of it is inability of the distal tubule reabsorb water If we assume that these patients are

insufficiency is all osmotic diuresis I do not think anyone can say I think the question that Dr Bradley raised earlier is a very good one that is is the urea concentration high enough to account for this degree of osmotic diuresis? In other words with a blood urea nitrogen of say 120 or 140 will we get out half of the glomerular filtrate? I cannot recall the exact figures but it is my impression that in dealing with urea diuresis in the dog one does not obtain so great an increase in urine flow from urea levels of this order of magnitude

Merrill We have to remember that that is in terms of perhaps 20 per cent or less of the nephron

Berliner I am talking about concentrations not total amount

Pitts Plasma concentrations

Berliner Now the question of whether there are other substances which may be retained by the anuric individual and which may contribute an osmotic effect to this diuresis I do not know but I doubt that there are enough of such materials to add very much to the effect of urea alone For these reasons I am inclined to think that although osmotic effect is a very important factor in the diuresis there are other contributory factors I suspect that one of the more important ones is some diminution in the capacity to reabsorb sodium and chloride

Bradley Dr Merrill has some data on the change in urea concentrations relative to variations in urine output

Berliner That is in patients with chronic nephritis One good way of investigating the role of osmotic diuresis in the polyuria following acute renal insufficiency would be by dialysis at about the time that diuresis is expected One could then observe whether reducing the urea concentration to a level which by itself does not produce diuresis would have any great effect on urine flow and sodium chloride excretion

Dock With the polyethylene tube technique in patients where we wished to obtain diuresis — say in cirrhotics or cardiacs — we could test the effect of giving from 60 to 70 per cent urea which is very soluble stuff Using a very small volume of water with the urea we could see what happened

Pitts Fundamentally what you wish to know is whether the flow load relationship per active nephron is the same in this condition as in the normal

Merrill Exactly

Pitts I do not see any way that we could possibly get at that

Lawson Why not give mannitol or para aminohippurate? These

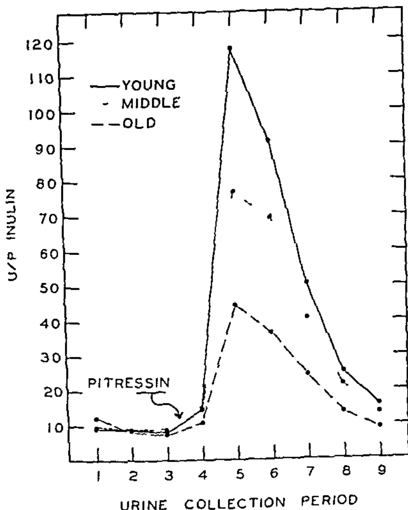


Figure 68. Mean values of U/P inulin ratio for each of three age groups before and after the intravenous administration of pitressin. Reprinted by permission from Miller, J. H. and Shock, N. W. Age differences in the renal tubular response to antidiuretic hormone. *J. Gerontol. 8*, 446 (1953).

under a considerable osmotic load excreting the dilute urine and 40 or 50 per cent of the filtrate, how much effect would we expect from pitressin? If we obtained none at all, we might say it was because the distal tubule was unresponsive On the other hand it might be capable of responding but fail to because of the preponderance of osmotic effect on flow I do not know what happens in pure osmotic diuresis when pitressin is given Do you Dr Berliner?

Berliner Pitressin produces relatively little change in urine flow when one is dealing with marked osmotic diuresis

Merrill So you could not distinguish between the two?

Berliner The effect we should expect would be small Whether or not we could detect it I do not know We can obtain a water diuresis superimposed on an osmotic diuresis due to urea and by giving pitressin detect a change in urine flow or in freezing point I am afraid, however, that in the diuresis following acute renal insufficiency, the probabilities are that we should not observe any effect because these patients have a failure of the ability to concentrate which is essentially equivalent to saying that we do not obtain much effect from the antidiuretic hormone

Merrill We did this a number of years ago and obtained no response to pitressin

Pitts It still does not answer the question

Shock The antidiuretic response to pitressin varies widely between individuals Dr John H Miller (12), working in our laboratory has been able to demonstrate a significant difference between the response of old and young subjects which we have interpreted as evidence for an age difference in tubular response to the antidiuretic stimulus The results in terms of U/P inulin ratios are summarized in Figure 38 Water diuresis was established by the administration of 500 ml of water at 6 a m , followed by 250 ml of water at half hour intervals until completion of the procedure After three ten minute control periods, pitressin (0 5 milli units per kg of body weight) was administered intravenously Subsequently six consecutive urine collection periods, each of 12 minutes duration were obtained The solid line shows average U/P values for nine subjects, aged from 26 to 45, the dotted line, mean values for ten subjects aged from 46 to 65, and the dashed line, ten subjects aged from 66 to 88 years The antidiuretic response of the older subjects is significantly less than that of the young in spite of the similarity of all age groups with respect to the original level of diuresis evoked A clearer impression of individual differences

tests Rough calculations indicate that to explain the variations on the basis of differences in solute excretion one would have to postulate unlikely values for total solutes

Bradley How many of the older people had urinary tract disease?

Shock Obviously, one can never be certain that disease does not exist in a given patient However none of the patients studied had clinically identifiable renal disease

EDITOR'S NOTE Dr Shock wishes to add the following explanation to his remarks at the conference

The criteria used for subject selection were (*a*) diastolic blood pressure less than 90 mm Hg (*b*) absence of clinical evidence of valvular disease (*c*) absence of cardiac enlargement in physical and teleoroentgenographic examination (*d*) absence of proteinuria in morning specimens by the heat acetic acid test (*e*) absence of abnormal findings on microscopic examination of sediment of fresh voided urine and (*f*) blood nonprotein nitrogen (NPN) less than 40 mg per cent

Dock Were the inulin excretion rates per square meter the same in these three groups or was the "glomerular filtrate falling?

Shock The glomerular filtration rate (GFR) diminishes with increasing age as shown in Figure 40 (13 14) Although the GFR is as low as 40 ml per 1 73 square meter per minute in some of our 80- to 90 year olds no elevation of NPN was found in these subjects nor were there any clinical signs of renal disease found The diminution in GFR with age is accompanied by a similar decrement in renal plasma flow as measured by diodrast or para aminohippuric acid (PAH) clearance so that the average filtration fraction remains constant over all ages

None of the patients included in the above studies had clinically diagnosable renal disease Of course the probability of having included some subjects with undiagnosable disease is greater in the older subjects than in the younger ones

Pitts In this connection if there is a reduction in number of functional nephrons I do not think you can say that there is necessarily any reduction in cellular ability to reabsorb water Inability to produce a high U/P ratio may be merely a consequence of relative osmotic diuresis in the remaining functional nephrons

Shock I do not believe there were any systematic age differences in the degree of osmotic diuresis In the first place the oral fluid intake was supplemented by the intravenous administration of 5 per cent dextrose in the infusion fluid administered during the

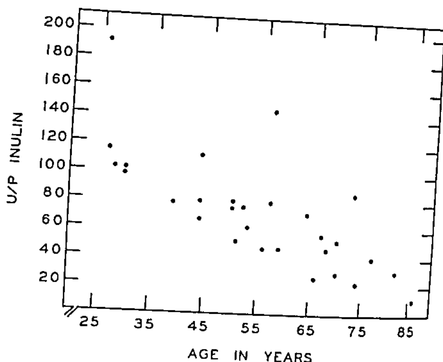


FIGURE 39 Following intravenous administration of pitressin relationship between maximum U/P inulin ratio and age Reprinted by permission from Miller J H and Shock N W Age differences in the renal tubular response to antidiuretic hormone *J Gerontol* 8, 446 (1953)

in the maximum antidiuretic response to pitressin may be seen in Figure 39

Pitts You really should have completed this with a study of newborns

Shock It is difficult for us to find newborns among our population

Lawson Measurements on the premature infant would probably fall somewhere between the lower two curves, and the mature new born infant would do better than the premature Were the diets and urinary solute excretions more or less the same in all of these people?

Shock Osmotic pressure of the plasma and urine were not measured in the present study, and conceivably there could have been an age difference in the total solute excretion However, the middle and old age groups were chosen from the same population and were receiving the same diets for many months prior to the

Pitts I said the improbable assumption

Dock Yes I know

Shock The basal metabolism of the older subjects is somewhat lower However both the middle and old groups of subjects were receiving the same diets

Bradley Will not pitressin evoke a less marked reduction of urine flow in the unilaterally nephrectomized dog?

Berliner Yes I cannot recall the details of the experiments but one group of investigators took out one kidney and as I remember also half of the other and found marked limitation of concentrating capacity

Pitts That is true of rats certainly

Dock Do you mean within a day?

Berliner I cannot recall all the details of the experiment but I think so *

Dock The daily osmotic load per nephron is doubled is it not?

Pitts Certainly but the animal is in balance

Berliner In some fashion animals treated that way come back to balance I do not know just what the adjustments are that make this possible but they are normal animals to all intents and purposes putting out what they take in Since they are eliminating the same amount through one quarter of the original number of nephrons each nephron must be putting out four times as much as the normal nephron

Shock In view of the similar reductions in GFR renal plasma flow (RPF) diodrast Tm and glucose Tm with age I think the physiological data are in agreement with the anatomical evidence that the older individual has lost functioning nephrons However I do not see how the differential responses to pitressin can be explained simply on the basis of a reduction in the number of functioning nephrons Note that in periods 1 2 and 3 of Figure 38 the response to hydration is the same in all age groups when measured by the U/P ratio of inulin that is consideration of the U/P ratio of inulin removes the influence of the difference in number of functioning units This difference does influence urine flow for instance If one assumes that the functioning units of old and young kidneys receive a supramaximal exposure to the pitressin administered the only way that the U/P ratio of inulin can be changed is by increasing the amount of water reabsorbed from the GFR It should be noted that the GFR did not change sig

*These statements have been checked and the essentials are correct The work referred to is that of Hayman *et al* (15)

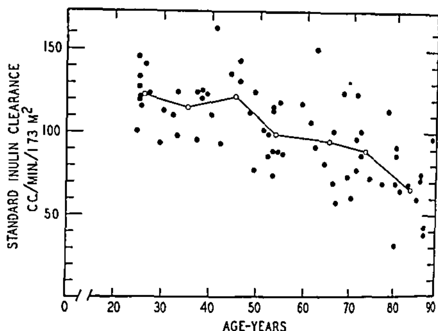


FIGURE 40 Change in standard inulin clearance with age Reprinted by permission from Shock N W Age changes in renal function *Cowdry's Problems of Ageing* A I Lansing Editor 3rd ed Baltimore Williams & Wilkins 1952 (p 614)

experiments The rate of infusion was 8 ml per minute Glucose excretion was measured in all periods but was negligible at the plasma levels reached The mean rate of excretion during maximum antidiuresis was 0 04 mm per minute Since there was no correlation between the rate of glucose excretion and either age or maximum U/P ratio of inulin attained after pitressin it seems evident that the glucose excretion had no measurable effect on the age differences in the antidiuretic effect

Pitts If we were to make the improbable assumption that milliosmolar excretory load were to remain constant then reducing the number of functional nephrons as a function of age would correspondingly reduce the response to pitressin

Berliner The solute excretion per nephron goes up?

Pitts Yes it goes up as the number of nephrons goes down

Dock The metabolism in all these older people is low as compared to the younger ones I should guess that their daily ingestion of electrolyte and nitrogen per square meter is considerably below the other group

Lauson I am merely trying to add other criteria to this kind of experiment, which might justify the statement that the individual distal tubules have diminishing response to pitressin in old age I do not know how they can be counted

Shock This is simply a reflection of the limitations of the clearance techniques with which we can determine only the over-all effects, we really want to know what goes on in individual nephrons

Dock. We can count the nephrons very easily at postmortem

Pitts We do not know whether they are functional though

Oliver It is a fallacy that they can be counted as functioning or nonfunctioning units We can count glomeruli, but we might include a good functional glomerulus, one that is no good at all, or one that is partially functioning There they all are, and they may look the same with ordinary means of observation

Dock Still, the initial count as to how many are there might be helpful.

Oliver It might give us a very false impression, because we might think we were counting something that could not be counted at all

Miller Dr Bradley, could your technique, showing the different lengths of nephrons, be applied profitably to the aged, to ascertain whether there was a change?

Bradley All it would show would be whether there was a change in the delay within the nephron population

Pitts This is really a reduction in number, though and in that case the delay should be reduced

Bradley It depends on the way in which reduction of the total number of nephrons affects the nephron population pattern

Pitts Proportionately

Bradley If the reduction in nephron population is a random affair, affecting all kinds of nephrons, then I see no reason at all why the distribution of delay should be altered in any way

We have measured delay between the glomerulus and the bladder in terms of the departure from equilibrium between the filtered load of inulin, or specific activity of radioactive isotope and excretion in the urine That is to say, the percentage of filtered load excreted during the first ten minutes after injection gives a value for the portion of the total nephron population having a ten-minute delay This figure is then used in calculating the proportion of nephrons contributing during the second collection period by ifference In computations of this kind (16), we have found that 0 per cent of nephrons contribute in the first ten minutes after

nificantly between the control periods and period 5 where the maximum U/P ratio of inulin was recorded Hence, I believe we have evidence that the functional capacity of the tubular cells to perform osmotic work on a unit of glomerular filtrate is impaired in the old kidney

EDITOR'S NOTE Dr Shock would like to add the following comments to his remarks at the conference

> Examination of the reference cited by Dr Berliner (15), showed that although the specific gravity of the urine excreted by dogs after subtotal nephrectomy diminished, these animals could excrete a concentrated urine under certain conditions, such as increased concentration of plasma colloids, lowered blood pressure and the administration of sodium sulfate after water deprivation

Pitts You have not changed the function of any single nephron's glucose Tm or the filtration rate, as far as the nephrons are concerned, all you are doing is altering the number of nephrons In that case, would you expect this to be the same result that you would obtain with pitressin?

Dock The osmotic load per nephron would go up

Lawson I think that kind of experiment ought to include, as a minimum, a determination of total solute concentration (milliosmoles per liter), and total solute excretion (milliosmols per minute), as well as urine flow and GFR Then comparisons could be made among individuals of different ages who have similar osmolar excretions per unit of GFR If differences in response to pitressin were still present after such calculations, I think it would establish this fact as well as could be done at the present time

Berliner However, we are not necessarily interested in the filtration rate, but the number of functional nephrons In other words, we do not know that doubling the filtration rate in one nephron has the same effect as doubling the number of nephrons and putting out the same amount of solute in either case

Lawson I added that it is the best we can do at the present time because we cannot count nephrons We can measure GFR, and if solute excretion rate and urine flow are calculated per unit of GFR, we can at least compare different individuals with respect to these data Of course, these calculations can give no assurance that the filtration rate per nephron is the same in all subjects, or within the kidney of any one subject

Pitts Is that any improvement on Dr Shock's idea of counting in terms of glucose Tm? It is merely an assumption on exactly the opposite side of the fence, it seems to me

Pressman How long is the intermittently active glomerulus supposed to be closed down in man? With our radioactive anti bodies in rats (20), we obtain essentially complete clearance from the blood of the antibodies within ten minutes say and we have always been able to obtain radioautographs of all the glomeruli in the field If there were glomeruli which were closed off we should expect to find some with no radioactivity in them However we have never seen any closed off I think by a quantitative measure ment of the amount of radioactivity in a glomerulus as could be determined by this radioautographic technique we might be able to determine whether some glomeruli were high and others low in localized radioactivity

Bradley I think we have really very little evidence that there is intermittency in the human kidney that is in the sense that filtra tion rate depends chiefly on the number of glomeruli operating at any one time I am not denying that the total number of glomeruli functioning in man may alter under appropriate circumstances such as shock or orthostasis but the view that the number of functioning glomeruli remains constant only because equal numbers begin and stop functioning from moment to moment is not supported by the anatomical or functional evidence

Pitts In place of carrying on this physiological discussion I think we should continue with Dr Bull and his story on acute renal failure

SOME ASPECTS OF THE PATHOGENESIS OF CIRCULATORY RENAL INSUFFICIENCY

Bull This condition is a far more common cause of acute renal failure than tubular necrosis It has been well established that a reduction in renal blood flow and glomerular filtration play an important role in causing the disturbance but very little seems to be known about the mechanisms that bring about the reduction It seems probable that inadequacy of the general circulation in some way sets off a train of events which results in reduction of renal blood flow glomerular filtration and retention of water and salt I shall call this the reaction to circulatory inadequacy

There are two main aspects to this problem first the way in hich circulatory disturbances initiate this train of events and econd the details of the effector are i e the actual mechanisms rectly affecting renal function It is the first that I wish to con ler The problem is linked with that of the control of body water

injection of the test substance 20 per cent in the second and 10 per cent in the third ten minute period In patients with renal insufficiency this distribution is displaced to the right We have had difficulty in interpreting our findings with radioactive sodium When para aminohippurate is given simultaneously with sodium *100 per cent or more of the radioactivity (by calculation)* seems to appear in the first ten minutes For a time we wondered whether this might be attributable to excretion of PAH as a sodium salt but we now believe that the phenomenon is probably the result of an abrupt change in sodium reabsorption secondary to the large dose of PAH In consequence there is increased sodium output and since this is derived from the newly filtered (labelled) sodium must necessarily have a higher radioactivity than it would if circumstances remained constant and radioactive sodium were diluted in the nonradioactive isotope

Bott I do not know whether it would help at all Dr Bradley but I was thinking of phenol red in connection with your comments on the PAH (17) I believe it is true that that is excreted as a salt in the proximal tubule I wondered if using that would give you any clue

Bradley What happens to the pH of the urine?

Bott I do not mean that it appears in the urine that way but as it comes through It may not have any bearing on the subject but I do know that when there is poor circulation through the glomeruli of an exposed kidney one sees a *general collapse of the* tubules and when the circulation becomes vigorous they swell up a little Perhaps that would help decide whether or not it is a pipe that you have

Bradley Do they collapse completely?

Bott No I should not say that

Grafflin At times in the frog there appears to be a severalfold difference in the caliber of the lumina under the two sets of conditions Also pertinent to the present problem is the great speed with which the provisional urine traverses the distal tubule when the frogs glomerular circulation is very active This was first observed by Ellinger and Hirt (18) and was subsequently confirmed by Singer (19) With poor glomerular circulation the forward movement of the urine proceeds much more slowly

Pitts Dr Bradley could these long delay nephrons by any chance be those that are intermittently active and which just happen to close down and wait for twenty minutes before they open up again?

Pressman How long is the intermittently active glomerulus supposed to be closed down in man? With our radioactive antibodies in rats (20) we obtain essentially complete clearance from the blood of the antibodies within ten minutes say and we have always been able to obtain radioautographs of all the glomeruli in the field If there were glomeruli which were closed off we should expect to find some with no radioactivity in them However we have never seen any closed off I think by a quantitative measurement of the amount of radioactivity in a glomerulus as could be determined by this radioautographic technique we might be able to determine whether some glomeruli were high and others low in localized radioactivity

Bradley I think we have really very little evidence that there is intermittency in the human kidney that is in the sense that filtration rate depends chiefly on the number of glomeruli operating at any one time I am not denying that the total number of glomeruli functioning in man may alter under appropriate circumstances such as shock or orthostasis but the view that the number of functioning glomeruli remains constant only because equal numbers begin and stop functioning from moment to moment is not supported by the anatomical or functional evidence

Pitts In place of carrying on this physiological discussion I think we should continue with Dr Bull and his story on acute renal failure

SOME ASPECTS OF THE PATHOGENESIS OF CIRCULATORY RENAL INSUFFICIENCY

Bull This condition is a far more common cause of acute renal failure than tubular necrosis It has been well established that a reduction in renal blood flow and glomerular filtration play an important role in causing the disturbance but very little seems to be known about the mechanisms that bring about the reduction It seems probable that inadequacy of the general circulation in some way sets off a train of events which results in reduction of renal blood flow glomerular filtration and retention of water and salt I shall call this the reaction to circulatory inadequacy

There are two main aspects to this problem first the way in which circulatory disturbances initiate this train of events and second the details of the effector arc i e the actual mechanisms directly affecting renal function It is the first that I wish to consider The problem is linked with that of the control of body water

and mineral content, and I shall mention some of the stimuli which are known to affect water and salt excretion

The osmoreceptor, posterior pituitary gland, and renal tubules form a sort of cycle which can regulate osmotic concentrations very adequately, but which cannot regulate total body water content Some other process must exist One possible mechanism for total body water regulation has been proposed by Sieker, Gauer, and Henry (21), and Drury, Henry and Goodman (22) They investigated the effects of breathing against positive and negative pressure Breathing against negative pressure seems in some way to alter the "set" of the osmoreceptor and give rise to a water diuresis whereas positive pressure breathing gives rise to an antidiuresis It seems very likely, as they suggest, that these effects result from reflexes arising in low pressure vascular circuits in the thorax The control of osmotic pressure, and the possible method of control of body water, is shown in Figure 41

A related phenomenon is the effect of breathing from 5 to 7 per cent of carbon dioxide This causes a diuresis and a fall in urine specific gravity, but without a significant change in ion or creatinine excretion (Figure 42)

The CO_2 diuresis is of the same type as that following the ingestion of water (23) There is the same delay in the onset of the diuresis and the absence of an effect on mineral excretion How

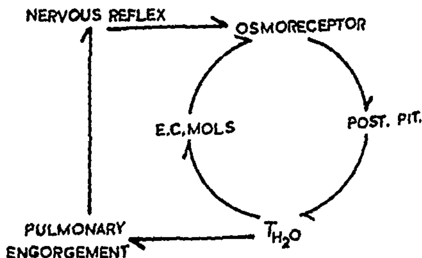


FIGURE 41 A possible system for regulation of body water

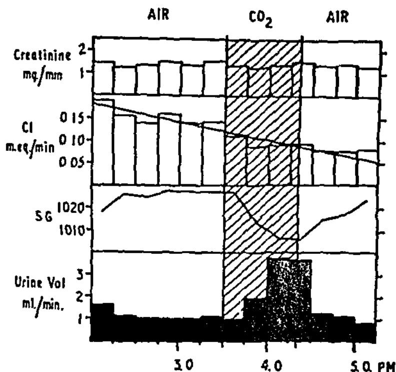


FIGURE 42 The effect of breathing from 5 to 7 per cent carbon dioxide on urine flow creatinine and chloride excretion and urine specific gravity in a recumbent normal subject. Note the delayed onset of diuresis and the absence of an effect on chloride and creatinine excretion Reprinted by permission from Barbour A Bull G M Evans B M Hughes Jones N C H and Logothetopoulos J The effect of breathing 5 to 7% carbon dioxide on urine flow and mineral excretion *Clin Sc* **12**, *1 (1953)*

ever, it differs in that a change in osmotic pressure of the plasma is not the effective stimulus to diuresis It is possible that the same mechanisms at work in the negative pressure breathing are at work here The increased ventilation associated with the CO_2 breathing could affect the same receptors However, if this were so we should expect a similar type of diuresis on voluntary hyperventilation, but this is not the case, as I will show later Whether the same pathways are involved or not, both negative pressure breathing and CO_2 breathing appear to induce diuresis by indirectly or directly altering the "set of the osmoreceptor, so that less pitressin is released for a given osmolar concentration than normally While it

could effectively control body water, it is very unlikely that the mechanism is involved in the regulation *of total body water under* ordinary conditions, simply because neither CO_2 nor negative pressure breathing affect glomerular filtration or sodium excretion significantly We have to look for another and dominant regulating system

This other system is almost certainly linked with the circulation in some way, because of the association of alterations in renal blood flow, glomerular filtration and water and salt excretion, with changes in the general circulation in heart failure, oligemic shock dehydration and so forth It seems to me that there are only two ways in which the altered circulation could be translated into a stimulus for water and salt retention or loss *first*, by causing a *chemical change due to a diminished* or increased flow *of blood to* the whole or a part of the body, or second, by causing pressure changes in some part of the circulation or in a body compartment

To consider the chemical changes first Changes in circulation could presumably result from changes *in cardiac output* which in turn, result from water and salt retention along the lines suggested by Borst (24) The changed circulation could then presumably alter the rate of transport to, or removal from, the tissue of a substance whose concentration would indirectly provide the signal of an altered state of hydration General changes in the rate of transport to or removal from, the tissues of any substance other than the blood gases, are unlikely to provide a signal for reaction to circulatory inadequacy, because the same pattern is seen in both high and low output cardiac failure When we examine the effects of altering blood gas concentrations we find marked changes

The effect of a raised pCO_2 *has already been dealt* with Hyperventilation with its fall in pCO_2, and slight rise in arterial pO_2, gives a different type of diuresis (Figure 43) Here, unlike the CO_2 diuresis, there is a prompt increase in urine flow, and an increased excretion of sodium and chloride (25)

Exactly the same pattern is seen on breathing 10 per cent oxygen Thus a fall in pO_2, and a rise in pCO_2, both cause diuresis, in the former with an increase in mineral excretion On teleological grounds we should expect the reverse if a change in blood gas concentrations were the signals we were seeking

However, it could be argued that changes in pCO_2, or pO_2 could *still be the stimulus if instead of considering the body as a* whole we considered the circulation in part of it For instance, both a rise in pCO_2, and a fall in pO_2, increase cerebral blood flow *Some*

could effectively control body water, it is very unlikely that this mechanism is involved in the regulation of total body water under ordinary conditions, simply because neither CO_2 nor negative pressure breathing affect glomerular filtration or sodium excretion significantly We have to look for another and dominant regulating system

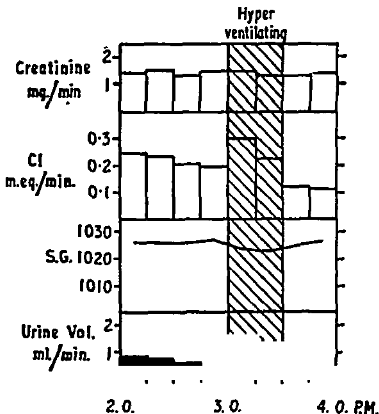
This other system is almost certainly linked with the circulation in some way, because of the association of alterations in renal blood flow, glomerular filtration, and water and salt excretion, with changes in the general circulation in heart failure, oligemic shock, dehydration, and so forth It seems to me that there are only two ways in which the altered circulation could be translated into a stimulus for water and salt retention or loss first, by causing a chemical change due to a diminished or increased flow of blood to the whole or a part of the body, or second, by causing pressure changes in some part of the circulation or in a body compartment

To consider the chemical changes first Changes in circulation could presumably result from changes in cardiac output which, in turn, result from water and salt retention along the lines suggested by Borst (24) The changed circulation could then presumably alter the rate of transport to, or removal from, the tissue of a substance whose concentration would indirectly provide the signal of an altered state of hydration General changes in the rate of transport to or removal from, the tissues of any substance other than the blood gases, are unlikely to provide a signal for reaction to circulatory inadequacy, because the same pattern is seen in both high and low output cardiac failure When we examine the effects of altering blood gas concentrations we find marked changes

The effect of a raised pCO_2 has already been dealt with Hyperventilation with its fall in pCO_2, and slight rise in arterial pO_2, gives a different type of diuresis (Figure 43) Here, unlike the CO_2 diuresis, there is a prompt increase in urine flow, and an increased excretion of sodium and chloride (25)

Exactly the same pattern is seen on breathing 10 per cent oxygen Thus a fall in pO_2 and a rise in pCO_2, both cause diuresis, in the former with an increase in mineral excretion On teleological grounds, we should expect the reverse if a change in blood gas concentrations were the signals we were seeking

However, it could be argued that changes in pCO_2, or pO_2, could still be the stimulus if instead of considering the body as a whole we considered the circulation in part of it For instance, both a rise in pCO_2, and a fall in pO_2, increase cerebral blood flow Some



change, consequent on this altered cerebral blood flow, might be the ultimate signal Somewhat in favor of participation of changes in cerebral blood flow in this regulating system is the fact that cerebral blood flow is reduced in quite a number of the sodium retaining states However, once again, the fact that CO_2 excess, the most powerful cerebral vasodilator causes no change in mineral *excretion renal blood flow, or filtration rate makes it extremely* unlikely that cerebral blood flow has anything to do with the regulating system we are seeking

There remains yet another possible way in which oxygen and carbon dioxide might be involved in a regulating system Changes in the concentration of either would affect the oxygen reduction potential (Eh) of tissues When both pO_2 and pCO_2 vary together, quite complex changes in Eh might occur I therefore decided to investigate the effects of Eh change on water and salt excretion

Very little seems to be known about tissue Eh, and particularly about methods of altering it The administration of three substances seemed worth considering as means of altering Eh, namely, ascorbic acid, methylene blue, and alpha tocopherol The first was excluded because it seems fairly well established that ascorbic acid plays some part in proximal tubule transport systems, so that any effect it may have might be directly on the kidney The other two were studied, and neither seemed to have any effect on water and salt excretion in the doses used

I shall show an example of the alpha tocopherol study only Figure 44 shows the design This was a normal subject, who for ten days was placed on an unvarying milk and biscuit diet, as used by Borst (26) The first four days were simply to allow equilibration on the diet, and on the fifth day, urine collections were started At intervals of four hours the patient received a glass of milk and a biscuit, and passed urine The urine concentration and the output of the various substances shown in the figure, were estimated on each sample On the 9th 10th and 11th days, one gram of alpha tocopherol was given per day Finally, the results were subjected to an analysis of variance, and the net result was that there was no significant change in excretion of any substance measured when tocopherol was given

Thus none of these attempts at discovering a chemoreceptor was successful In fact, while this work was in progress, a paper by Petersdorf and Welt (27) appeared, on the effect of infusion of hyperoncotic albumin on excretion of water and solutes which seemed to me to be important in that it made any chemical stimulus whatever very unlikely Iso oncotic expansion of plasma volume causes a sodium and water diuresis which would be in keeping with its effect of increasing cardiac output and plasma volume However, the same expansion and presumably the same circulatory change induced by hyperoncotic albumin, gives an antidiuresis It would seem then, that any chemical effect of an improved circulation would be extremely likely, because the two have quite the reverse effects Therefore, I think it will be more profitable to seek a baro receptor, rather than a chemoreceptor, for this regulating system

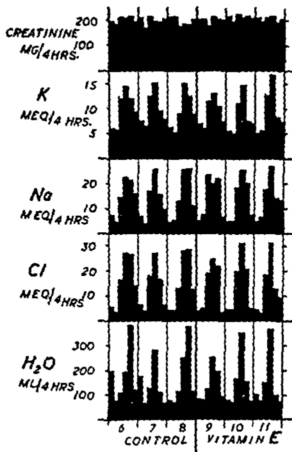


FIGURE 44 The absence of effect of administering 1 gm per day of alpha tocopherol on water and mineral excretion (Roche Products Ltd kindly supplied the vitamin E)

To take up the second point there are so many possible sites at which a pressure change might act, that I do not propose to consider very many A general venous pressure change seems to be very unlikely, for example, sodium retention occurs in both oligemic shock and congestive heart failure, conditions in which the pressure moves in opposite directions Furthermore, even in congestive heart failure, there does not seem to be a very good correlation between retention and venous pressure

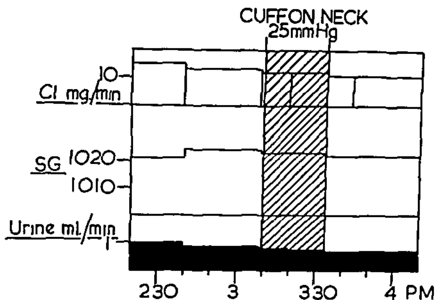


FIGURE 45 The absence of effect of application of a venous occluding cuff to the neck of a sitting normal subject

Changes in general arterial pressure are also unlikely to provide the signal because in mild oligemic shock or with light venous cuffing in the recumbent subject, obvious sodium retention may occur without obvious blood pressure fall (Figure 45) Furthermore, in left ventricular failure with pulmonary edema the blood pressure may be elevated or depressed, but sodium retention and very severe renal blood flow reduction are uniform

There is some evidence that the receptor we are seeking is intracranial, or has such a component If intracranial pressure change are the signals, we can further narrow the field on the results of studies in which the pressure is lowered by the removal of cerebrospinal fluid This maneuver does not appear to affect the excretion *of water or solutes as Fishman has shown (28), and Barbour and* I have confirmed (29) Thus if there is a baroreceptor in the head it does not seem very likely that it will be in a low pressure intracranial site However the possibility of one in a high pressure site i e in an artery remains

Throughout I have assumed that the stimulus to sodium retention etc is the same in all conditions This I think is possible but it may be incorrect If it is correct I think that the most likely receptor for sodium control is a baroreceptor, for the reasons I have

given and possibly the site would be intracranial or a high pressure spot in the thorax I hope that this may draw some others who are working in this field to discuss the matter

Bradley I agree wholeheartedly with this analysis of the factors that may be involved in control of salt and water excretion It is certainly true that analysis of the factor of pressure change is difficult Too frequently it is forgotten that all measurements of pressure variation are necessarily incomplete The blood pressure may alter from beat to beat and the important change may be transient and escape detection because the compensatory readjustments it evokes occur so rapidly The readjustments persist however and may be important in producing other physiological alterations For example in shock vasoconstriction persists in the kidney when the vascular dynamics have been restored to normal Thus changes in electrolyte excretion in association with variations in filtration and presumably also in association with humoral and neural release might very well reflect the action of a stimulus which is no longer detectable or measurable that is indeed past history Hence a baroreceptor system seems the more likely agent through which changes in volume are mediated

Dock Dr Bull in the experiments Dr Drury (22) made with breathing against pressure hyperventilation occurred During this the leg volumes began to swell very promptly as soon as pressure breathing was begun There is no doubt but that that sort of pressure breathing increases the volume of ventilation and at the same time changes the gradient from the periphery to the heart so that there is a high peripheral venous pressure both in the head and feet The intrathoracic pressure increases the water from 8 to 10 cm This has an effect on the cardiac output and flow and on the pressure on the renal vein The Drinker respirator lowers pressure in the chest and tends to increase the cardiac output This is about the same as the overventilation induced by CO

Bull Carbon dioxide is different from ordinary hyperventilation t is CO like breathing against negative pressure will give a :e water effect whereas hyperventilation with presumably the ne mechanics produces a water and salt effect

Dock Hyperventilation produces alkalosis almost instantly does not whereas CO gives the patient a little acidosis? I do not know hat the negative pressure breathing does or how much we over entilate with this We could increase the cardiac output that way i think without increasing the ventilation nearly as much as we do with the positive pressure Dr Drury uses This is a varying positive

pressure The patient breathes out against one pressure, and is refilled at a higher pressure The volume of the legs begins to increase instantly There is a slow increase while sitting and breathing normally, and as soon as the pressure breathing is begun, the slope of the leg volume goes up In Dr Drury's experiments, they were dehydrating the blood stream of the patients, and obtaining a rising hemoconcentration by producing an edema in the lower part of the body, at any rate

Bull The positive pressure breathing produces all kinds of complicating effects which might be influencing the circulation everywhere, but the negative breathing produces a different sort of effect from that which one ordinarily obtains from altering circulation as such It produces a pure water type of diuresis, which is quite different, for example, from infusion of saline, iso-oncotic plasma or blood

Dock Of course, Dr Harrison's (30) view was that all this could easily be demonstrated by putting a cuff around the neck and blowing it up and the postural changes and antidiuresis could be abolished if we used the cuff and maintained a good headache by high venous pressure inside the head Nobody has ever confirmed that, have they?

Bradley No

Dock So that does not seem to wear very well At any rate, the levels of venous pressure that he was using produced a headache, and an undoubted severe cerebral engorgement, and had nothing to do with what occurs in cardiacs Were these patients sitting up?

Bull Yes

Dock Harrison had such complicated conditions of water loading and hydration that the results were dubious

Berliner I do not like to bring up this question because it is one that has been argued many times, and no one knows the right answer, but I wonder how much change in filtration rate one would have to find to account for a drop in sodium excretion in the order of magnitude of that found by Petersdorf and Welt (27 [illegible]

Bull I do not think that is impo[illegible] efferent end that [illegible] anything else [illegible]

Berliner I [illegible] hyperoncotic albumin does not reduce fil[tr]ation rate [illegible] is the signal?

Bull Oh, I see!

Berliner If we are measuring only endogenous creatinine clearances, and allowing for an error of plus or minus 10 or 15 per cent,

I am sure that the tools are not sharp enough to do the job I am all in favor of the idea of baroreceptors or whatever you may wish to call them but I do not think I should discard the other possibilities on the basis of that particular experiment

Dock You thought that pulmonary engorgement for instance might be the baroreceptor?

Bull It is possible that that pulmonary engorgement affects a baroreceptor of some sort changing only water excretion The negative pressure breathing and CO_2 were possibly affecting the set of the osmoreceptor as it were altering the level at which antidiuretic hormone (ADH) would be excreted from that system However it could not be regulating total body water simply because that sort of experiment is not affecting sodium excretion at all

Dock It is surprising that sodium diuresis results from breathing 10 per cent oxygen is it not?

Bull Yes but responses to hyperventilation 10 per cent oxygen and positive pressure breathing are all exceedingly complicated

Dock Congenital cardiacs with low arterial oxygen tensions do not seem to have any trouble at all as far as water sodium and so forth are concerned They may have been adapted over a period of years to this I do not know But it is striking in this experiment Does one overventilate very much with 10 per cent oxygen?

Bull Yes a bit

Dock But compared with CO_2 it is negligible?

Bull That is right

Dock A very striking thing to see this sodium excretion double The one thing that seems to be certain is that when the cardiac output falls or goes very high it is inadequate they say for the patient s needs This machinery then goes into play in opposite directions in shock and in congestive heart failure

Bull In opposite directions as far as venous pressure is concerned but in the same direction as regards the reaction to circulatory change The effect of the changed circulation is unlikely to be mediated through a fall in rate of transport of anything other than the blood gases to the tissues because both high and low cardiac output produce the same pattern

Dock In some tissues it might be increased but it could very well be that in a cirrhotic with a high cardiac output and heart failure there would be a blood flow through the central nervous system that was not quite as good as it should be I do not know whether this would be measured in cerebral blood flow and high output cardiac failure but I should guess it was down a little bit

Bull In the type of high output cardiac failure which is observed in emphysema, it is definitely up

Dock The cerebral flow is well up?

Bull Yes

Dock With arterial anoxia?

Bull Yes, and due to the high pCO_2

Pitts I do not follow this last conclusion You had baroreceptors either intracranial or at some high pressure site in the thorax What do you mean by that, and why?

Bull A low pressure site in the head is unlikely to be the sensitive area, because cerebrospinal fluid (CSF) removal does not appear to affect water and salt excretion but there is, as I said some evidence to implicate the head If the sensitive area is in the head it must be in a high pressure site

From pressure breathing experiments it is probable that there is a baroreceptor in the low pressure intrathoracic circuit, but this cannot be the one we are seeking, because of the absence of salt effects There might be another receptor in a high pressure site which does affect sodium

Dock Apparently all conceivable variations on the theme have been tried, but an explanation of the phenomenon has not been found

Bull The changes in blood gases have nothing to do with it, we have tried them all

Luetscher From a clinical standpoint, it is difficult to work out a common denominator for all these factors

Dock Dr Bull s common denominator is all right, as far as it goes

Luetscher Except that it does not define anything

Pitts It is descriptive and not analytic?

Berliner A good deal of it is assumption

Dock After all we are dealing with a hypothesis

Berliner Dr J G G Borst has not measured the changes in cardiac output which he assumes are important factors in sodium excretion While in shock and other such extreme situations, it is obvious that the cardiac output must be reduced, however, there are a number of other changes in sodium excretion which he attributes to variations in cardiac output, but he conceives that such changes in output would be too small to measure

Dock There are a good many processes in that section of the human organism The change in CO_2 that makes one take a breath is not very easy to measure either I think everyone admits that

there is some relation between CO_2 tension and breathing but it becomes very complicated mainly because in exercise we begin overbreathing before the CO_2 tension changes take place

Bradley I think everyone admits that the volumes of fluid in the body are kept relatively constant and that the kidney is integrated into the body economy in such a way that it subserves this general goal But then where are we? It seems to me it is much more likely that the human organism contains a very complex system of checks and balances

Dock A group of receptors

Bradley They come into play in one way or another depending on the situation In disease perhaps these systems are disturbed

Luetscher I think that Dr Bradley s point is a very fundamental one The volume and composition of extracellular fluid is an important system which must be regulated by a variety of factors We have seen a number of mechanisms demonstrated here which can alter sodium excretion each of which must play some part in the regulation of sodium balance The chance of finding one signal which sets all these mechanisms into play is very remote I think we should concern ourselves with the factors involved in the particular system we are interested in it is difficult to keep from being confused by the other experimenter s system Many factors which decrease the sodium retaining activity of the urine in human disease also increase glomerular filtration

Dock There is normally a morning sodium diuresis is there not Dr Bull?

Bull Yes the peak is about midday

Dock Even though one is on one s feet?

Bull Yes

Dock Has this been tested out on patients with Addison s disease who because of inadequate treatment are on the verge of crisis? It would be interesting to see to what extent the machinery would break down

Luetscher One group studied the effect of posture on sodium in at least one Addisonian patient retention was much reduced

Dock The postural sodium retention was absent I wonder whether the noon sodium excretion was also gone?

Luetscher Other circumstances enter into it

Dock They have a good sodium excretion

Burnett The normal diurnal water rhythm may be entirely reversed in the Addisonian disease patient and this can be corrected

Pitts It is exactly the same But if you combine this with 5 per cent CO breathing you will not see that This is not known it is a hyperventilation response

Dock Hyperventilation is associated with an increased sodium output so presumably this might be related to washing out base to balance the acid CO eliminated in the lungs

Pitts It correlates very nicely with the CO regardless of the type of hyperventilation i e with a pump or from CO inhalation It follows the pCO not the volume of air breathed

Bull One of the most puzzling things in tubular necrosis is why we obtain a reduction of renal blood flow for a very long time After a year or even three years the renal blood flow can be sub normal

Dock In young people?

Bull Most of them are within the 20 to 30 year age group

Lauson What is the incidence of infarction in this kind of kidney? The reason I ask is that we applied renal artery clamps for two hours in three dogs In all three some degree of infarction was evident at autopsy about four months later renal function had not returned fully to normal (34)

Bull I do not know I think that infarction is probably made quite to explain it Figure 46 is a biopsy done at about 40 days after onset It was an open biopsy so there was about one square centimeter by about two or three millimeters of tissue There were only two damaged nephrons like that in the block

Dock The percentage was very small?

Bull Yes

Dock But there could have been cortical necrosis elsewhere in that same pair of kidneys

Bull Yes but we saw and felt the whole kidney to find the most suitable part to study

Dock There were no signs of any scar?

Bull No we examined the spot most likely to reveal damage but that was all we saw

Swan Was the size of the kidney approximately normal?

Bull Yes

Dock This is the first time acute cortical necrosis has been mentioned during two days devoted to the kidney We are really doing very well At any rate none of your cases was believed to have had acute cortical necrosis and none of them had hematuria of any severe degree when they began?

Bull This one did not but keep in mind that this patient had



FIGURE 46. Biopsy of kidney 40 days after onset of tubular necrosis

the right condition for developing a cortical necrosis She had concealed accidental hemorrhage then had a period of oliguria lasting eight days, and this was taken at about the 40th day

Merrill What about the inulin clearance at that time?

Bull I do not know Renal plasma flow was about 60 per cent normal

Merrill And in the other patients?

Bull There is considerable variation in the rate of return of function in these people but at a month, the mean RPF would be about 50 per cent normal

Breed Did you have an extraction ratio around the time of the biopsy?

Bull In this patient, we had extraction ratios earlier, i e , 36 per cent on the 4th day, and 60 per cent on the 19th day

Oliver Was the extraction ratio high enough to make you believe that the renal blood flow assumption was valid?

Bull Yes, because by then it was probably better than 60 per cent

Oliver If the extraction were only 60 per cent, how much confidence would you place in the procedure as a measure of renal blood flow?

Bull A limit could be put on the error that would be introduced Instead of 60 per cent of normal flow, it could be anything from normal down to, say, 30 per cent or something like that But even if we took a figure of 30 per cent of normal renal blood flow, we should find only a very small percentage of nephrons that were damaged

Oliver But why take 30 per cent? Why not take the other extreme that you mentioned 100 per cent?

Bull Yes, I see what you mean

Pitts Were the renal blood vessels that you considered all normal in this biopsy?

Bull Yes

Bradley Was there any evidence of hypertension?

Bull No

Bradley Do you know whether the blood flow will increase in response to a vasodilator stimulus?

Bull No, I do not know

Oliver I was wondering if, functionally, these vessels were peculiar in some way They might look all right, but there may have been some state of contraction

Dock You would use pyrogen to release them?

Bradley I was thinking of something a little more safe, something like apresoline, i e hydrazinophthalazine

Dock Have any of these conditions been studied at postmortem? Apparently the patients who had this prolonged decrease in renal flow also had a decrease in glomerular filtrate

Swan Prior to Dr Bull's study, most investigators claimed that a complete restoration of renal function took place The subjects were usually patients exposed to carbon tetrachloride or other chemical toxins, which, according to Dr Oliver, usually produce a type of injury characterized by a diffuse lesion in the proximal tubule, but

relatively little of the tubulorhexic lesion In the main, I think Dr Bull's series of cases includes those in which, according to Dr Oliver, one sees a greater preponderance of the tubulorhexic lesion Such an irreversible lesion might be expected to result in decreased inulin and PAH clearances

Oliver There do not seem to be enough of what you call "tubulorhexic lesions"

Bull· That is correct, there was just one

Oliver In general, the tubules do not look like damaged tubules

Dock If there had been a good deal of intrarenal extravasation of urine, there might be some change of connective tissue particularly in its rigidity

Oliver. Except that there is only one good streak of scar tissue

Bull No, we found another one

Dock Streaks like this might not work well and perhaps would not be able to expand

Oliver You had only one biopsy did you not? You are not certain as to how many there might have been in the kidney?

Bull That is right

Oliver Of course, if every field had a streak of connective tissue like that, and one damaged glomerulus How large was this biopsy?

Bull About one square centimeter by three millimeters

Oliver Oh, well, that would not knock out very many would it?

Dock It is not a question of what is eliminated, but of how rigid the supporting structure might become and the capacity of the kidney to expand at each heart beat, which apparently is quite an important thing Here, however, there was none of the hypertension that would be expected with a kidney that could not expand — the sort of thing one observes in perinephritis In the end Dr Oliver I think you will have to find out what this disease is anatomically I suspect there is an anatomical lesion here that reduces the potential blood flow through the kidney in these cases

Oliver I agree that it is a possibility but in this particular example, it does not seem to be definite from the evidence we have

Pitts In Figure 46, is that a glomerulus, all nicely hyalinized there?

Bull Yes, it is

Pitts That is the one place in the whole biopsy where you really found something?

Bull Yes

Dock Two places in a square centimeter, or better It would be *interesting to perfuse these kidneys with kerosene and see what* their postmortem perfusibility would be, it usually approaches the pyrogen figures for para-aminohippurate clearance in living patients *The calculated flow of blood would be over two liters to a pair of* normal young kidneys

The next thing would be to inject the kidneys with a good lead gelatin mixture, so that the sections would show us what the blood vessels really looked like

Oliver That would not give us an accurate idea of where the blood was flowing during life

Dock It would show us the possible bed as compared with the possible normal vascular bed With arteriosclerotic patients for example, *it is very striking how different the kidneys look* when one is injected and each vessel is fixed at the largest lumen it could ever have had during life One may look extraordinarily vascular in many cases of hypertension, and the other unusually avascular, because each artery is in rigor and has no lumen Some hypertensive kidneys have vessels which are hypertrophied, so the wall looks thick and there is no lumen But as soon as the *kidney sections* are filled with gelatin that is chilled at 100 mm Hg pressure in the system, then the wall of the artery can scarcely be found, and the lumen is wide *I think it is worth while to study these vessels* morphologically, especially when we are worried about the blood flow We can study the vascular bed This is all very easily done, *and it does not require any complicated apparatus Anybody can* make up a gelatin mass and raise the pressure in the perfusion system to 100 mg of mercury

Bradley The reduction in the extraction ratios certainly suggests that blood is perfusing more nonextracting tissue than in the normal kidney

Dock Yes, that we are almost sure of

Berliner That extraction ratio was determined at some earlier time, was it not?

Bull Yes The other extractions suggest that it was probably normal by them

Bradley You have no data on maximal transfer rates?

Bull Yes, a few data on glucose Tm's Sirota (35) has data on PAH Tm's in carbon tetrachloride poisoning

Oliver Is it correct to say that most of the people who have acute tubular necrosis do ultimately reestablish normal function, but that a certain per cent — and I should be interested to know what per

ent — do not? Apparently, there is some difference in opinion on ıat matter

Bull Only one of our patients was within the normal range at ne year

Oliver Did you make any observations after a year?

Bull Yes Dr Lowe did some at about two or three years

Lauson The statements in the earlier literature that kidney func on recovers completely in these cases were based chiefly on results f the phenolsulfonphthalein (PSP) test which is inadequate to etect slight to moderate reductions of function

Merrill We followed 14 of these patients with very much the ame results as Dr Bull We have not done biopsies on them

Dock There were no hypertensives in that group were there?

Merrill No

Oliver A considerable number never returned to normal?

Merrill Only one of the 14 got back to normal

Bull Lowe s figures (36) on our patients (Table XII) were much he same

We have reason to believe that the extractions would be normal o long after onset

Lauson Was the same trend observed when the inulin clearance er Tm ratios was considered?

TABLE XII

Time after Onset (in Years)	Effective Renal Plasma Flow (ml per min)
1½	204
2½	497
2¼	475
2	388
2½	533
2¼	266
1½	390
¾	381
¾	332
3	474
2¼	505
½	326
½	355
1¾	248

Bull The Tm's were not done during the latest follow up examinations The glomerular filtration came up a little better than the PAH clearance In one patient, for example, with a blood flow of 204 at two years, the thiosulfate clearance was 80 ml per min

Burnett Are they able to concentrate the urine?

Bull Yes

Oliver Dr Bull, would you care to describe the cases of chronic ulcer you have observed that seem to eliminate a few nephrons each time there is an alkalotic episode, and what the significance of such a series of episodes might be in the end?

Bull I have wondered whether recurrent attacks of tubular necrosis might eventually produce a contracted kidney Figure 47 shows a patient in whom this might have occurred He had a peptic ulcer for years, and had taken large quantities of alkali In addition he had recurrent episodes of severe vomiting and weakness, and was admitted in one such attack On admission he was dehydrated and had a blood urea of 600 mg per 100 ml On rehydration he

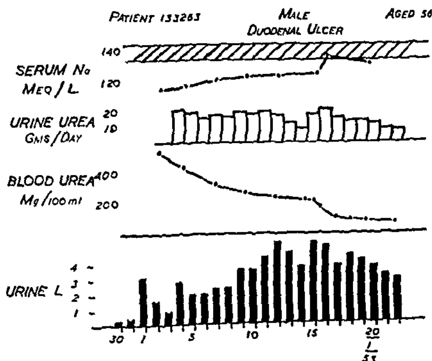


FIGURE 47 Data from a patient with peptic ulcer and renal failure

behaved very much like a patient with tubular necrosis In particular, on January 15th, there was a change in the rate of fall of his blood urea, and a rise in serum sodium which was not associated with any abrupt change in creatinine clearance I interpreted this as an improvement in tubule function His endogenous creatinine clearance leveled off at about 10 ml per minute, and he lived for a year and a half after this episode, dying just before I left London Macroscopically, the kidneys were very contracted I wonder whether he, and other people like him might not develop contracted kidneys as a result of repeated attacks of tubular necrosis

Oliver Had he been doing this before?

Bull Yes, he had I just wondered whether some of these people with chronic contracted kidneys, in association with alkalosis and vomiting, do not just knock off a few nephrons each time they have an attack

Burnett To my knowledge, nobody has ever demonstrated such a patient with normal renal function prior to this series of episodes Therefore, I do not believe we can possibly answer this question Until a patient with initially normal kidney function is observed who then goes on to terminal renal failure, I do not think we can safely talk about the so-called alkalotic kidney

Dock Would subjecting a dog to repeated injuries throw any light on this?

Burnett I know of no good evidence

Dock Work along those lines has not been done on dogs

Swan Dr Oliver, how long does it take for the tubulorhexic lesion to be converted into a scar?

Oliver There is no reason why fibrosis, and even hyalinization cannot take place fairly rapidly, that is within a week or so I have always thought it would take a long time, but I think we have been disillusioned by recent work

Dock Some very interesting experiments (37 38) were done in Portland on hobos who took lethal doses of carbon tetrachloride together on the same day and who died seriatim Silver and collagen stains were used to determine the length of time it took them to develop new connective tissue Proliferating argentophil material could be seen in a few days

Luetscher Dr Bull, it was intimated in the previous discussion that the diuretic phase following acute renal failure may be, in a sense, an artefact which might be produced by a rigid plan of fluid replacement For example adding the urine volume of the previous day to the basal water requirements, might give an unnecessarily

there has been the idea that back diffusion plays a part in the production of low clearances, and that the clearance of PAH, corrected by the extraction ratio, results in a fairly high *renal blood flow*

Bull Nevertheless, these blood flows, done with extractions showed a reduction

Breed So the implication is that there is an actual ischemia present?

Bull Yes

Oliver There certainly is experimentally, if we administer enough mercury to the dog or rabbit I think it is a matter of degree If we give a very small amount of mercury, as we do therapeutically, we do not obtain necrosis of tubules If we give a higher concentration, we can produce the pure necrosis With still larger doses, we can produce both necrosis of tubules and ischemia (39) I think we demonstrated this in living animals And then, too, human beings are very different from animals If we poison a rabbit, he just quietly and decently lies down and dies If a person takes bichloride, he goes through an awful procedure How he could escape getting a reflex renal ischemia, I do not know, what with the retching and vomiting, to say nothing of the mental agony A psychiatrist might suggest that there may be a psychosomatic element in the renal lesion of human bichloride poisoning

Miller The psychosomatic difficulty usually precedes the poisoning [illegible] comes [illegible] would [illegible] o there is a double trauma

REFERENCES

1 OLIVER J Structural and functional relationships in the kidney *Ciba Foundation Conference on the Kidney* (In press)

2 SHEEHAN H L, and MOORE, H C *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage* Oxford, England Blackwell Scientific Publications, 1952

3 KAPLAN, S A and FOMON, S J Function recovery pattern in acute renal failure following ingestion of mercuric chloride *Am J Dis Child* 85, 633 (1953)

4 BULL, G M JOEKES, A M, and LOWE, K G Renal function studies in acute tubular necrosis *Clin Sc* 9, 379 (1950)

5 BLACK, D A K Renal factors in volume control of body fluid *Ciba Foundation Conference on the Kidney* (In press)

6 DE OLIVEIRA H L *Excretion of ammonium in cases of acute tubular necrosis with acidosis and alkaline urine* *Metabolism* 2, 36 (1953)

7 SWAN R C and MERRILL J P The clinical course of acute renal failure *Medicine* 32, 215 (1953)

8 BULL G M JOEKES A M and LOWE K G Conservative treatment of anuric uraemia *Lancet* 2 229 (1949)

9 MOORE, F D HALEY H B BERING E A JR BROOKS L and EDELMAN I S Further observations on total body water II Changes of body composition in disease *Surg Gynec & Obst* 95, 155 (1952)

10 ENGEL, F L Further observations on the role of the adrenal cortex in the metabolism of amino acids *Endocrinology* 49 538 (1951)

11 MATHE G Fluid balance in acute renal insufficiency *Ciba Foundation Conference on the Kidney* (In press) (1953)

12 MILLER J H and SHOCK N W Age differences in the renal tubular response to antidiuretic hormone *J Gerontol* 8 44[illegible] (1953)

13 DAVIES, D F and SHOCK N W Age changes in glomerular filtration rate effective renal plasma flow and tubular excretory capacity in adult males *J Clin Investigation* 29 496 (1950)

14 SHOCK N W Age changes in renal function *Cowdry's Problems of Ageing* A I Lansing Editor 3rd ed Baltimore Williams & Wilkins 1952 (p 614)

15 HAYMAN J M JR SHUMWAY N P DUMKE P and MILLER M Experimental hyposthenuria *J Clin Investigation* 18 195 (1939)

16 BRADLEY S E NICKEL J F and LEIFER E The distribution of nephron function in man *Tr A Am Physicians* 65, 147 (1952)

17 CHAMBERS R and KEMPTON R T Indications of function of the chick mesonephros in tissue culture with phenol red *J Cell & Comp Physiol* 3 131 (1933)

18 ELLINGER P and HIRT A Mikroskopische Untersuchungen an lebenden Organen zur Funktion der Froschniere (Die Ausscheidung des Fluoreszeins in der Froschniere) *Arch f exper Path & Pharmakol* 145, 193 (1929)

19 SINGER E Observations on the frog's kidney with the fluorescence microscope *Am J Anat* 53 469 (1933)

20 PRESSMAN D EISEN H N and FITZGERALD P J The zone of localization of antibodies the rate of localization of anti mouse kidney serum *J Immunol* 64 281 (1950)

21 SIEKER H O GAUER O H and HENRY J P The effect of negative pressure breathing on renal function *J Clin Investigation* 31 572 (1952)

22 DRURY D R HENRY J P and GOODMAN J The effects of continuous pressure breathing on kidney function *J Clin Investigation* 26 945 (1947)

23 BARBOUR A BULL G M EVANS B M HUGHES JONES N C H and LOGOTHETOPOULOS J The effect of breathing 5 to 7% carbon dioxide on urine flow and mineral excretion *Clin Sc* 12 1 (1953)

there has been the idea that back diffusion plays a part in the production of low clearances, and that the clearance of PAH, corrected by the extraction ratio, results in a fairly high renal blood flow

Bull Nevertheless, these blood flows, done with extractions, showed a reduction

Breed So the implication is that there is an actual ischemia present?

Bull Yes

Oliver There certainly is experimentally, if we administer enough mercury to the dog or rabbit I think it is a matter of degree If we give a very small amount of mercury, as we do therapeutically, we do not obtain necrosis of tubules If we give a higher concentration, we can produce the pure necrosis With still larger doses, we can produce both necrosis of tubules and ischemia (39) I think we demonstrated this *in living animals And then, too, human beings are very different from animals If we poison a rabbit, he just* quietly and decently lies down and dies If a person takes bichloride, he goes through an awful procedure How he could escape getting a reflex renal ischemia I do not know, what with the retching and vomiting, to say nothing of the mental agony A psychiatrist might suggest that there may be a psychosomatic element in the renal lesion of human bichloride poisoning

Miller The psychosomatic difficulty usually precedes the poisoning

Oliver Oh no, there are two psychic crises The major one comes after the person has taken the poison and has decided that he would prefer to live, after all and realizes that he has no chance So there is a double trauma

REFERENCES

1 OLIVER, J Structural and functional relationships in the kidney *Ciba Foundation Conference on the Kidney* (In press)

2 SHEEHAN H L, and MOORE, H C *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage* Oxford, England, Blackwell Scientific Publications, 1952

3 KAPLAN, S A and FOMON, S J Function recovery pattern in acute renal failure following ingestion of mercuric chloride *Am J Dis Child* 85, 633 *(1953)*

4 BULL G M, JOEKES, A M, and LOWE, K G Renal function studies in acute tubular necrosis *Clin Sc 9, 379 (1950)*

5 BLACK, D A K Renal factors in volume control of body fluid *Ciba Foundation Conference on the Kidney* (In press)

6 DE OLIVEIRA H L Excretion of ammonium in cases of acute tubular necrosis with acidosis and alkaline urine *Metabolism* 2, *36 (1953)*

7 Swan R C and Merrill J P The clinical course of acute renal failure *Medicine* 32 215 (1953)
8 Bull G M Joekes A M and Lowe K G Conservative treatment of anuric uraemia *Lancet* 2, 229 (1949)
9 Moore F D Haley H B Bering E A Jr Brooks L and Edelman I S Further observations on total body water II Changes of body composition in disease *Surg Gynec & Obst* 95 155 (1952)
10 Engel F L Further observations on the role of the adrenal cortex in the metabolism of amino acids *Endocrinology* 49, 538 (1951)
11 Mathe G Fluid balance in acute renal insufficiency *Ciba Foundation Conference on the Kidney* (In press)
12 Miller J H and Shock N W Age differences in the renal tubular response to antidiuretic hormone *J Gerontol* 8 446 (1953)
13 Davies D F and Shock N W Age changes in glomerular filtration rate effective renal plasma flow and tubular excretory capacity in adult males *J Clin Investigation* 29 496 (1950)
14 Shock N W Age changes in renal function *Cowdry's Problems of Ageing* A I Lansing Editor 3rd ed Baltimore Williams & Wilkins 1952 (p 614)
15 Hayman J M Jr Shumway N P Dumke P and Miller M Experimental hyposthenuria *J Clin Investigation* 18 195 (1939)
16 Bradley S E Nickel J F and Leifer E The distribution of nephron function in man *Tr A Am Physicians* 65, 147 (1952)
17 Chambers R and Kempton R T Indications of function of the chick mesonephros in tissue culture with phenol red *J Cell & Comp Physiol* 3, 131 (1933)
18 Ellinger P and Hirt A Mikroskopische Untersuchungen an lebenden Organen zur Funktion der Froschniere (Die Ausscheidung des Fluoreszeins in der Froschniere) *Arch f exper Path & Pharmakol* 145, 193 (1929)
19 Singer E Observations on the frog's kidney with the fluorescence microscope *Am J Anat* 53 469 (1933)
20 Pressman D Eisen H N and Fitzgerald P J The zone of localization of antibodies the rate of localization of anti mouse kidney serum *J Immunol* 64 281 (1950)
21 Sieker H O Gauer O H and Henry J P The effect of negative pressure breathing on renal function *J Clin Investigation* 31 ((2 (1952)
22 Drury D R Henry J P and Goodman J The effects of continuous pressure breathing on kidney function *J Clin Investigation* 26 945 (1947)
23 Barbour A Bull G M Evans B M Hughes Jones N C H and Logothetopoulos J The effect of breathing 5 to 7% carbon dioxide on urine flow and mineral excretion *Clin Sc* 12 1 (1953)

24 Borst, J G G The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride, an essential factor in the genesis of oedema *Acta med scandinav (supp 207)* 130, *1 (1948)*
25 Stanbury S W, and Thomson, A E Diurnal variations in electrolyte excretion *Clin Sc* 10, *267 (1951)*
26 Borst, J G G, and de Vries, L A The three types of natural diuresis *Lancet* 2, *1 (1950)*
27 Petersdorf, R G, and Welt, L G The effect of an infusion of hyperoncotic albumin on the excretion of water and solutes *J Clin Investigation* 32, *283 (1953)*
28 Fishman R A The failure of intracranial pressure volume change to influence renal function *J Clin Investigation* 32, *847 (1953)*
29 Barbour, A and Bull, G M In discussion on renal factors in volume control of body fluid *Ciba Foundation Conference on the Kidney* (In press)
30 Lewis, J M, Jr, Buie, R M, Sevier S M, and Harrison, T R Effect of posture and of congestion of the head on sodium excretion in normal subjects *Circulation* 2, *822 (1950)*
31 Burnett, C H Seldin, D M, and Walser, M Observations on the electrolyte and water metabolism in Addison's disease during oral salt loading *Tr A Am Physicians* 66, *65 (1953)*
32 Howarth, S Cardiac output in osteitis deformans *Clin Sc* 12, *271 (1953)*
33 Smith H W *Studies in the Physiology of the Kidney* Lawrence Kansas City, School of Medicine, Univ Kansas Press, 1939 (p 85)
34 Roof B S, Lauson, H D, Bella, S T, and Eder, H A Recovery of glomerular and tubular function including p amino
occlusion

35 man, the mechanisms of renal failure and recovery *J Clin Investigation* 28, *1412 (1949)*
36 Lowe K G The late prognosis in acute tubular necrosis *Lancet* 1, *1086 (1952)*
37 Peery T M Carbon tetrachloride poisoning, study of stages of hepatic damage and repair in man *Arch Path* 26, *923 (1938)*
38 Moon H D The pathology of fatal carbon tetrachloride poisoning with special reference to histogenesis of hepatic and renal lesions *Am J Path* 26, *1041 (1950)*
39 Oliver, J MacDowell M, and Tracy, A The pathogenesis of acute renal failure associated with traumatic and toxic injury Renal ischemia nephrotoxic damage and the ischemuric episode *J Clin Investigation* 30, *1305 (1951)*

INDEX

C

H

I

Index

H

I

H

I

S